Clinical Evaluation of Thalamic Deep Brain Stimulation for Movement Disorders in Multiple Sclerosis

Julie Ellen Hooper

Doctor of Philosophy

The University of Edinburgh

2000

Declaration

I, Julie E. Hooper, hereby certify that this thesis:

(a) has been composed by myself

and

(b) that the work contained is my own, excepting those areas wherein the work of others is acknowledged.

Acknowledgements

It is impossible to mention by name all those who have helped me in the course of this project. I would like to thank all of the patients and their families for their help in participating in the study. I am also grateful to the MS Society of Great Britain and Northern Ireland for funding this research.

I would like to thank Dr Brian Pentland and the staff in the Brain Injury Research Unit at Astley Ainslie Hospital and my colleagues in the Department of Clinical Neurosciences who were a constant source of support. Particular thanks to Dr Robert Taylor and Mr Michael Glasby for their proof reading and invaluable comments.

Special thanks must go to my supervisors: Professor Ian Whittle who set this project underway and whose immeasurable enthusiasm and involvement were crucial throughout; Dr Brian Durward for his unstinting advice and constructive comments.

Lastly I would like to thank my friends and family whose support has been unwavering. I would like to thank my parents for their love and constant support, my children Aimée and Ewan for providing numerous distractions often when I didn't need them and my husband Ian for his encouragement and constant presence which helped me through my darkest moments. Without him this thesis would not have been completed.

Abbreviations

ADL activities of daily living

AC anterior commissure

AMPS Assessment of Motor and Processing Skills

BRW Brown-Robert-Wells

BI Barthel Index

CNS central nervous system

CT computerised tomography

CSF cerebrospinal fluid

CBFS Cerebellar Functional Systems

clinical exam clinical examination

DBS deep brain stimulation

DCN Department of Clinical Neurosciences

DIP Disability Impact Profile

ESS Environmental Status Scale

EDSS Expanded Disability Status Scale

ET essential tremor

FIM Functional Independence Measure

FSS Fatigue Severity Status Scale

FS functional scale

FDS Fatigue Descriptive Scale

FTRS Fahn's Tremor Rating Scale

FAMS Functional Assessment of Multiple Sclerosis Quality of Life Instrument

Goal trem goal-related tremor

HAD Hospital Anxiety and Depression Scale

HQ Handicap Questionnaire

Hz Hertz

ICIDH International Classification of Impairment Disability and Handicap

IPG implantable pulse generator

JTHF Jebsen Test of Hand Function

JEBPRE total Jebsen score pre-operatively

JEBON1 total Jebsen score at 1 month with the DBS on

JEBON3 total Jebsen score at 3 months with the DBS on

JEBON6 total Jebsen score at 6 months with the DBS on

JEBON12 total Jebsen score at 12 months with the DBS on

JEBOFF1 total Jebsen score at 1 month with the DBS off

JEBOFF3 total Jebsen score at 3 months with the DBS off

JEBOFF6 total Jebsen score at 6 months with the DBS off

JEBOFF12 total Jebsen score at 12 months with the DBS off

Kin/int kinetic/intention tremor

kHz kiloHertz

LOS length of stay

LHS London Handicap Scale

MRI magnetic resonance imaging

MS multiple sclerosis

MFTRS Modified Fahn's Tremor Rating Scale

mm millimetres

MDMS movement disorders due to multiple sclerosis

MD movement disorder

MSQOL-54 Multiple Sclerosis Quality of Life Instrument

NHS National Health Service

On1m assessment with the deep brain stimulator on at 1 month

On3m assessment with the deep brain stimulator on at 3 months

On6m assessment with the deep brain stimulator on at 6 months

On12m assessment with the deep brain stimulator on at 12 months

Off1m assessment with the deep brain stimulator off at 1 month

Off3m assessment with the deep brain stimulator off at 3 months

Off6m assessment with the deep brain stimulator off at 6 month

Off12m assessment with the deep brain stimulator off at 12 months

PC posterior commissure

PR primary-relapsing

PP primary progressive

Pre-op pre-operatively

Posta) trem postural a) tremor

Postb) trem postural b) tremor

Pour water pouring water

QENF quantitative tests of neurological function

Rest trem rest tremor

RR relapsing-remitting

SP seconday-progressive

s seconds

TRIG Tremor Investigating Group

UK United Kingdom

USA United States of America

VL ventrolateral

VIM ventro-intermediate

VOP ventral-oralis posterior

V volts

WHO World Health Organisation

Table of Contents

TABLES

FIGURES

ABSTRACT

Disorders of movement are recognized features of multiple sclerosis (MS). They often involve the upper limbs, head and trunk and can prevent a person from carrying out the simplest of daily activities such as holding a drink and feeding themselves. This may have enormous psychological consequences, often leading to frustration, embarrassment (particularly in social situations), withdrawal and increased dependence on others.

Treatment of these disorders of movement, which are usually refractory to medical therapy, has been by thalamotomy, a neuroablative technique. Results have been variable and often unsatisfactory in the long term. Recently thalamic deep brain stimulation (DBS) has been proposed after its successful use in the treatment of Parkinsonian tremor. Relatively little information exists on the use of this treatment in patients with MS. Studies carried out so far have been on very small cohorts and have used non-validated outcome scales and short follow-up. There is little data on the effect of the movement disorder on a person's disability, handicap and quality of life (QOL); the perception of ability after surgery; and on the costs involved in thalamic DBS.

The work presented here had 3 principal objectives: first to develop and validate a scale for measuring movement disorders in MS (MDMS); secondly to evaluate the effect of thalamic DBS on impairment, disability, handicap and aspects of quality of life (QOL) relevant to these patients; and thirdly to estimate the costs associated with thalamic DBS.

The Modified Fahn's Tremor Rating Scale (MFTRS) was developed and validated for the purposes of this study. Results of the validity, reliability and responsiveness of the MFTRS, as given in the published paper, showed that it can be used with confidence in the clinical setting.

Thirty seven patients with MDMS were assessed before operation. Fifteen patients underwent thalamic surgery. The target arm was assessed 1, 3, 6 and 12 months after operation using the MFTRS, which measured severity of tremor, and the Jebsen Test of Hand Function (JTHF) which measured performance of 7 subtests of upper limb function. Information concerning the influence of the movement disorder on overall disability, handicap and QOL was collected at or over 12 months and was compared with that of the pre-operative assessment using various subjective rating scales and questionnaires.

Results showed that thalamic DBS significantly reduced the severity of tremor amplitude and significantly improved performance of the Jebsen subtests when the DBS was on at each post-operative assessments (1, 3, 6, and 12 months) compared with pre-operatively (all p values < 0.02). However, these symptomatic and changes in function did not translate into significant improvements in patients' performance in activities of daily living and thus there were no apparent economic benefits (ie. savings in future care-costs). Also there was no change in patients' perceptions of their handicap or in most aspects of QOL: the only significant change was that patients perceived themselves to be less anxious 12 months after the operation ($p=0.03$). The overall impact was therefore clinically limited.

This prospective study has illustrated the benefits and limitations of thalamic DBS in patients with MDMS, and has highlighted the post-operative rehabilitation and follow-up requirements and the resulting health economic implications associated with its use. The validation of the MFTRS not only enabled the effect of thalamic DBS to be evaluated but also provided a major contribution to the assessment of MDMS.

CHAPTER 1

STEREOTACTIC NEUROSURGERY FOR MOVEMENT DISORDERS IN PEOPLE WITH MULTIPLE SCLEROSIS

1.1 Multiple Sclerosis (MS)

1.1.1 What is MS?

Multiple Sclerosis (MS) is primarily a disease of young adults (Ebers and Sadovnick 1997) of unknown aetiology. It is an acquired primary demyelinating disease of the central nervous system (CNS) in which myelin is the target of an autoimmune inflammatory process. Demyelination refers to the acquired damage, whatever the cause, to apparently normal myelin (Whitaker and Mitchell 1997) .

Primary demyelination implies that the myelin unit, comprising the oligodendrocyte and CNS myelin sheath, is the pathogenic site of injury. In contrast, secondary demyelination occurs when the axonal components are damaged so that the requisite signal from the axolemma for myelin formation or maintenance is lost. Although the axon is relatively spared in MS accounting for its designation as a primary demyelinating disease, the axon can be affected, especially in later phases.

In 1993, a distinguished group of neurologists reached concensus on a classification which has gained widespread acceptance for diagnosing MS in clinical practice, epidemiology and treatment trials (Poser et al. 1983). The Poser criteria link natural history and physical findings for the diagnosis of MS and define the age of onset range as 10-59 years. The clinical manifestations of MS typically appear between 20 and 45 years of age (Riise 1997) with focal, multifocal, episodic and general neurological signs and symptoms (Whitaker and Mitchell 1997) .

MS has two clinical hallmarks which occur after the first episode of neurological deficit. The first is the often sudden appearance of further neurological deficits, called a relapse or exacerbation, followed by a more gradual disappearance of the symptoms, or restoration of function, known as remission. By definition, a relapse lasts at least 24 hours and cannot be attributed to any other cause, especially fever (Lublin and Reingold 1996). The severity of the relapse is highly variable and relates to the area and the volume of the CNS tissue damage. The gradual appearance of neurological deficits, referred to as progression, may be associated with or substituted for relapses and remissions, giving rise to different disease subtypes and courses. It is the progressive deficit, which might also be viewed as the failure of remission, that accounts for disability, handicap and decline in quality of life (QOL) in MS.

The second hallmark of the disease is the dissemination of lesions anatomically within the CNS. On the basis of whether one or both of these two clinical hallmarks are present and whether one or more paraclinical abnormality can be demonstrated by cranial or spinal magnetic resonance imaging (MRI), evoked potential or

cerebrospinal fluid (CSF) testing, MS is diagnosed into definite MS and probable MS, each with two subgroups, clinical and laboratory supported (Poser et al. 1983).

1.1.2 Incidence and prevalence of MS

To understand the epidemiology of MS it is necessary to define the terms incidence and prevalence. The incidence rate is the most informative measure of disease frequency and is simply the number of new cases within a period i.e. one year, divided by the number of individuals at risk of developing the disease during the same period. It is usually expressed as the number of cases per 100,000 population. The annual incidence of cases with MS is 4 per 100,000 (Baum and Rothschild 1981)

.

In MS the calculation of incidence is complicated by several factors. Although the goal is to find the number of cases who develop the disease during each year, the only figure that might be observed during a year is the number of cases who receive a diagnosis. Only a few cases will receive a diagnosis during the same year as they first experienced symptoms of the disease. The rest will be observed during the following years. The diagnosis of MS is often uncertain in the early stages and there is an acknowledged time lag from clinical onset of MS to diagnosis which averages 4 years (Ebers and Sadovnick 1997).

The generation of reliable incidence data on MS is therefore related to a number of difficulties and therefore most studies investigating the frequency of MS have aimed only at ascertaining all patients who have the disease at the particular date of the study. This gives the prevalence rate, which is defined as the number of cases in a

population who, at some fixed point in time, have the disease relative to the total population at the time of the study. The prevalence rate is easier to obtain since it can be calculated directly, based on present information. However, it is not a very good measure of the risk of developing the disease in the population under study as it is subject to factors such as survival and migration, which can bias the results.

There is considerable variation in the prevalence of MS around the world (Compston and Sadovnick 1992). Cross-cultural epidemiological studies have found a significant correlation between prevalence rates and geographical latitude, with the higher prevalence rates occurring further away from the equator (Silberberg 1977). Multiple sclerosis has a prevalence of approximately 100 per 100,000 population in most parts of the United Kingdom (UK), northern Europe, northern United States of America (USA) and Canada (Compston and Sadovnick 1992). In the UK, epidemiological studies have shown prevalence rates of between 99 per 100,000 (Roberts et al. 1991) and 178 per 100,000 (Swingler and Compston 1988), putting this country firmly in the high prevalence category. MS affects approximately 1.1 million people worldwide (Dean 1994) and women are more susceptible than men by a factor which is at least 1.5:1 (Kurtzke 1991) .

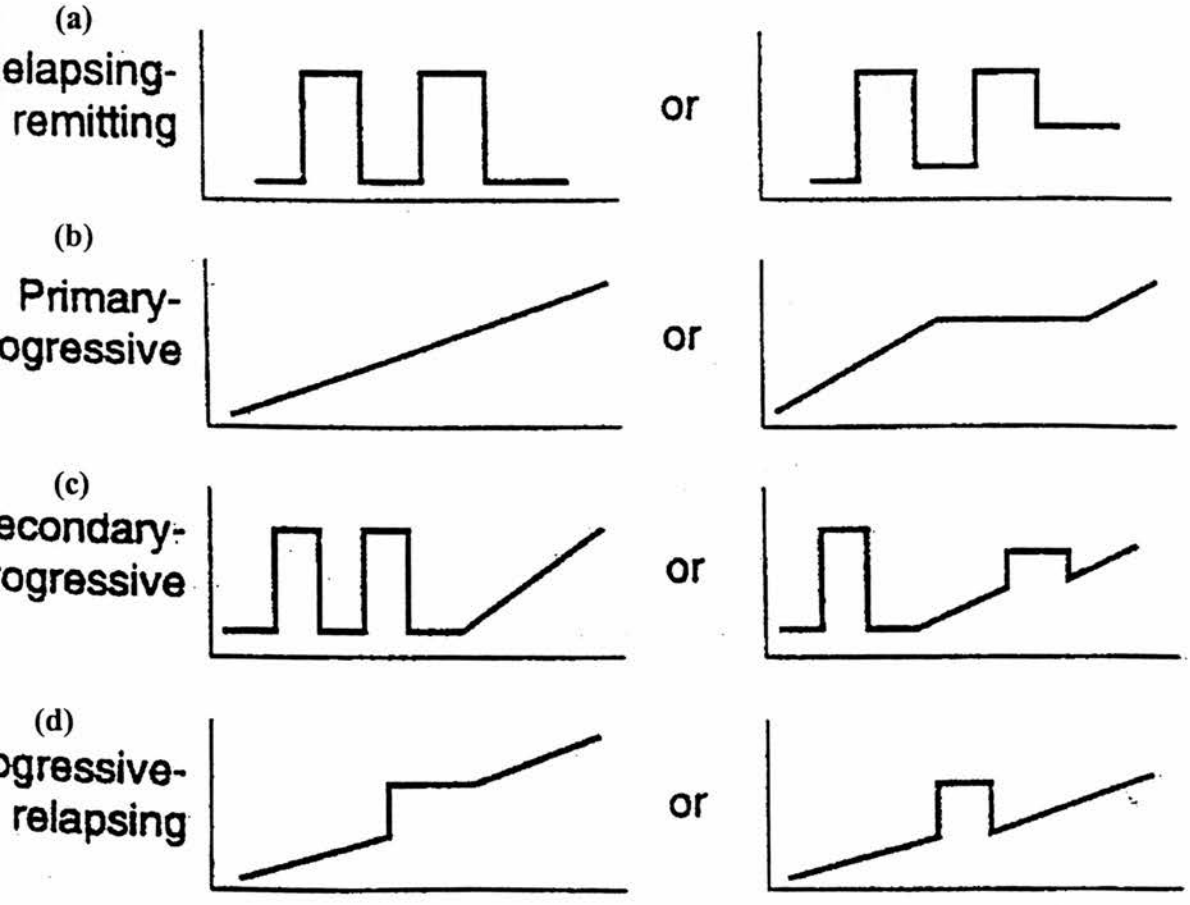
1.1.3 Clinical subtypes of MS

The multiplicity of neurological deficits, the relative mix of relapses and remissions with or without overall progression and the severity of the disease leads to a marked clinical heterogeneity of the population of individuals accurately diagnosed with MS (Matthews 1988). MS has generally been described in terms of a series of disease

states – relapsing-remitting (RR), relapsing-progressive (RP), secondary-progressive (SP) and primary-progressive (PP), the definitions of which have been subject to considerable controversy. In an effort to standardize the terminology used for MS subtypes, an international survey (Lublin and Reingold 1996) led to the following classification which is depicted graphically to show the evolution of MS-related impairment over time:

Figure 1-1: Four different courses of MS

These are the relapsing-remitting (RR), primary-progressive (PP), secondary-progressive (SP) and progressive-relapsing (PR) subtypes (Lublin and Reingold 1996) .



a) Relapsing-remitting (Figure1-1a); clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery. Periods between disease relapses are characterized by a lack of disease progression.

b) Primary-progressive (Figure1-1b); disease progression from onset with occasional plateaus and temporary minor improvements.

c) Secondary-progressive (Figure1-1c); initial RR disease course followed by progression with or without occasional relapses, minor remissions and plateaus.

d) Progressive-relapsing (Figure 1-d); progressive disease from onset, with clear acute relapses, with or without full recovery, with periods between relapses characterized by continuing progression.

In addition to this classification and the possible combinations of relapses, remissions and progression, the same survey addressed the accepted usage of the terms used to denote clinical severity. Benign MS is defined as disease which allows a patient to remain fully functional in all neurologic symptoms 15 years after onset of the disease. Malignant MS is characterized by rapid, progressive course, leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset.

The clinical course is highly variable (Silberberg 1977): about 20% of people with MS experience a benign course and are only mildly affected throughout their lives; at the other extreme, about 10% of patients present with a primary progressive (malignant) form of the disease (Shannon 1999) . This latter group of patients tends to be older at onset than the others (Graham 1999) , deteriorate rapidly and can have

a shortened life span (McDonald and Thompson 1997) . The RR state is encountered in approximately 70% of MS patients, the RP variety in 15% and the PP variety in 15% (Weinshenker 1997). Of those with RR disease, roughly 50% will have converted to a SP form of MS within 10 years (Runmarker and Andersen 1993;Weinshenker et al. 19969) . Furthermore the pathologic changes in MS may be asymptomatic.

1.1.4 Clinical symptoms of MS

MS not only has a variable clinical course but also has a variable presentation between patients. Highly diverse signs and symptoms arise from CNS damage and the consequences of slowed or blocked conduction in axons (Matthews 1988) . In spite of the fact that demyelination may occur essentially anywhere within the CNS, the majority of patients have their initial symptoms in a relatively limited distribution. The Gottingen study of 812 cases of MS (Bauer 1978) identified the most common symptoms at presentation and during the course of the disease as listed in the table below:

Table 1. 1: Multiple sclerosis-symptoms at presentation and during the course of the disease

Deficit reported	Initial presentation (%)	During course (%)
Visual/oculomotor (diplopia)	49	100
Paresis	43	88
Paraesthesia	41	87
Brainstem/cerebellar	23	82
Genito-urinary/Bowel	10	63
Cerebral	4	39

Loss of vision, strength or sensation are the typical initial manifestations of MS as can be seen from Table 1-1, and ataxia occurs more commonly during the course of the disease. For those patients who present initially with cerebellar signs

> 'the early appearance of cerebellar ataxia indicates poor prognosis and cerebellar signs are frequently persistent without significant remission' (Matthews 1988).

It is also uncommon for a patient to develop an isolated cerebellar syndrome. More commonly, cerebellar signs occur with a multiplicity of other findings which usually include sensory disturbance, weakness and, possibly, brain stem signs (Matthews 1988) .

The results of the Gottingen study (Bauer 1978) confirmed the well known information that most frequently observed symptoms arise from damage to major white matter tracts and present as unilateral or bilateral visual loss (optic tracts), hemiparesis (pyramidal tracts), ataxia (cerebellar connections) and internuclear ophthalamoplegia (internuclear brainstem connections) (McAlpine et al. 1955).

This study addressed the specific problem of movement disorders due to multiple sclerosis (MDMS) and not other symptoms of MS and therefore these will not be considered further.

1.1.5 A framework for measuring the effect of tremor on impairment, disability and handicap

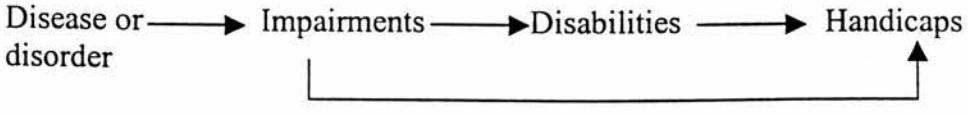
1.1.5 (i) The International Classification of Impairment, Disability and Handicap

In 1980 the World Health Organization published the first version of the International Classification of Impairments, Disabilities and Handicaps (ICIDH

1980) as a classification of disablement and functioning which systematically grouped the 'consequences of disease' into 3 'dimensions' the definitions for which are: losses or abnormalities of bodily function and structure (formerly impairments), limitations of a person's activity (formerly called disability), and restrictions in participation in society (formerly called handicap). Although the terminology in the ICIDH-2 (1997) has been changed the new terms are not yet widely known or accepted and therefore for the purpose of this thesis they are still referred to by the former terms of impairment, disability and handicap.

The overall disablement phenomena were visualised as follows in the 1980 version of the ICIDH:

Figure 1-2: Relationship between impairment, disability and handicap as depicted in ICIDH 1980:



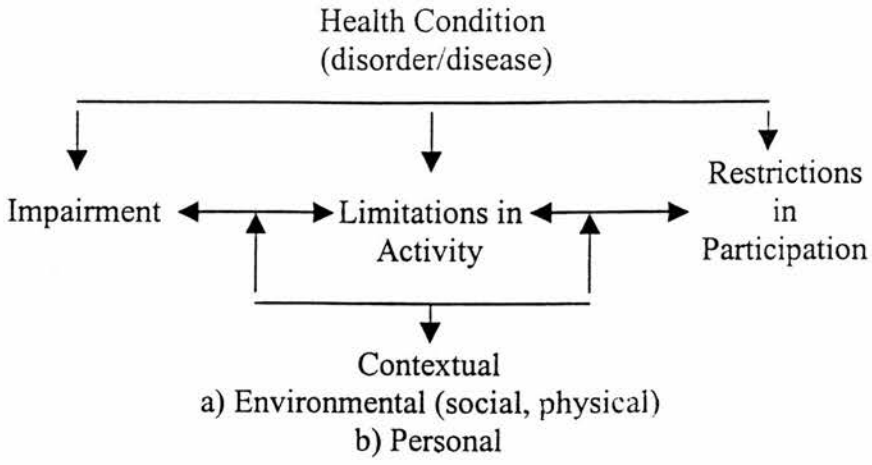
The original text suggests a degree of linearity by presenting each dimension graphically leading to the next as shown in Figure 4-1. There is no doubt that the representation of the model above was over-simplified as it implied a *unidirectional flow* from impairment, to disability, to handicap. However, the relationship between dimensions is clearly more complex in that alteration at a structural level may not lead to disability (i.e. functional consequences of an impairment do not necessarily arise). Further, extensive handicap may occur with apparently minimal disability.

Another criticism of the 1980 ICIDH model was that it did not adequately reflect the role of the social and physical environment in disablement but perpetuated a solely medical view of disability. Authors such as French and Swain acknowledged that disabled people have rejected the notion that their difficulties arise from individual impairment but believe instead that disability is socially created by the many physical and social barriers which exist within society (French and Swain 1997)

It is now recognized that the impact of ill health is not solely dependent on the impairments, disabilities and handicaps which result from it but on other contextual factors also. The ICIDH-2 (1997) has recently been designed which includes a list of contextual (environmental and personal) factors, which all have an impact on ill health. Environmental factors can be further sub-divided into social and physical factors and include social attitudes, laws, policies, architectural characteristics, legal and social structures, as well as climate, terrain and so forth; and personal factors include sex, age, other health conditions, coping styles, social background, education, profession, past and current experience, overall behaviour pattern, character style and other factors that determine how disablement is experienced by the individual.

In order to avoid misinterpretations that that were induced by the ICIDH 1980 diagram a current understanding may be presented as in Figure 1-3.

Figure 1-3: Current understanding of interactions within the ICIDH-2 dimensions:



The diagram shows that disablement and functioning are outcomes of interactions between health conditions and contextual factors. The interaction is complex, bi-directional and dynamic. The model does not place a causal linkage between the three dimensions of disablement and functioning; rather they occur within each of the three dimensions of impairment, disability (now called activity) and handicap (now called participation) and by means of contextual factors.

The subjective satisfaction with life is called 'quality of life' (QOL). There is a lot of debate about whether or not QOL is an entirely different entity from handicap, or is merely the same entity viewed from a different perspective. The two terms can be differentiated by considering handicap as the objective or externally assessed social consequences of a health condition, whereas QOL life measures the patient's subjective impression of their state of affairs. An important aspect of the present study was to establish the patients' perceptions of the outcome of the intervention as

there is a dearth of information in this area. However research into QOL is less well developed than that concerning impairment or disability and many difficulties remain in its measurement (Fallowfield 1990; Rothwell 1998) . Many researchers believe that the term 'quality of life' refers to an illusion that cannot be defined and therefore cannot be measured (Wade 1992) . Wade argues that a solution to this problem is to be explicit about the aspects of QOL that are important and relevant to the research in question and to measure them individually.

1.1.6 The impact of MS on impairment, disability, handicap and quality of life

The most obvious manifestation of MS is neurological impairment and as discussed above a wide range of impairments can occur in MS.

> 'The attraction of thinking about disease in terms of impairments is that it is often these impairments that are the targets of treatment; they are the means by which severity is usually measured, and they help in monitoring the patients' progress. The very success of the biological approach to disease has tended to blinker clinicians to other possible views.' (Ebrahim 1991)

However, there is now an awareness that treating the biological consequences of disease is not enough and that impairment has a major impact on disability and handicap. Many patients with MS have a normal life span and have to live with some degree of disability over a prolonged period which can dramatically affect the level of handicap and the quality of life experienced by afflicted patients and their families.

For patients with chronic, incurable diseases such as MS, the main objective of an intervention may be to lessen the impact of disease, to enable the sufferer to realise his potential within the limitations imposed by the disease and to reduce the

disadvantage experienced as a result of ill-health. The framework suggested by the ICIDH-2 (1997) allows evaluation of the achievement of such an objective.

MDMS often affect the upper limbs and can interfere with or prevent a person from carrying out the simplest of daily tasks (Matthews 1988) such as blowing one's nose, holding a drink, or feeding oneself. Even mild upper limb tremor can also affect a variety of other activities such as balance and walking, home making or driving and therefore can result in increasing dependence on others. This has enormous psychological consequences, often leading to frustration, anger, embarrassment and withdrawal, especially since the MDMS are extremely difficult to treat.

Several other factors make MS a disease with important psychological and social implications which can cause restriction in social participation. First its unpredictable nature makes it difficult for patients to gain a sense of control over their illness. Second MS typically affects young adults (Ebers and Sadovnick 1997) , thereby limiting their most productive years (Bourdette et al. 1993) . Thirdly as no cure is available patients must rely on treatments which only alleviate symptoms and slow disease progression (Jacobs et al. 1994; Johnson et al. 1995) . Also the disease although limiting to the patient may not be readily apparent to others. This contributes to a sense of isolation experienced by many people with MS (Murray 1995) .

Handicap is defined in the ICIDH as the disadvantage for any given individual, resulting from impairment or disability, that limits or prevents fulfilment of a role

that is normal (depending on age, sex, social and cultural factors). People have many different roles such as being a partner, a parent, a friend, a wage earner and many more. Thus the level of handicap is defined by the social environment of the individual and how their own specific environment interacts with their impairment or their disability. A given set of impairments and disabilities will not lead to the same handicaps in every patient. In this way, handicap emphasises the uniqueness of each person, and the need for a unique response.

Many authors have proposed that not only disabilities and the influence of disabilities on the life of the patient (handicap) but also the subjective satisfaction with life as judged by the patient should be used to reflect the impact of diseases on the lives of individuals (Fallowfield 1990) . As already mentioned the subjective satisfaction with life is called 'quality of life' (QOL). It is an important area of research as in the management of chronic diseases such as multiple sclerosis for which cure is not possible but death is a remote outcome, the key goal of health care is often to reduce handicap and optimise a patient's quality of life.

In this study, palliative thalamic DBS was carried out in the hope not only of reducing the severe movement disorder of an upper limb (impairment) in an attempt to improve functional use of the limb but also to enable the person to participate in simple activities of daily living at a personal level (disability) and also at the level of society, thereby reducing the level of handicap. The study also aimed to address the patient's perception of the outcome as there is a dearth of information in this area. Multiple measures of outcome were therefore used within the framework of the ICIDH-2, which will be discussed in detail in Chapter 4.

1.2 Movement Disorders in Multiple Sclerosis (MDMS)

The tremor of multiple sclerosis is often a component of a complex disorder of movement referred to as ataxia. Ataxia and tremor occur commonly and the movement disorder often includes dysmetric and other ataxic features (Hallet et al. 1985) which are due to the involvement of the cerebellar pathways. Serial dysmetria has been described as 'successive inaccurate movements producing the appearance of irregular tremor' (Sabra and Hallet 1984) and 'the result of the voluntary sequential correction of movement errors' (Hallet 1986) .

Cerebellar and/or brain stem involvement or both is seen in 82 % of cases of MS at some time during the course of their illness (Bauer 1978) as was shown in the Gottingen study involving 812 patients with MS. In a three year follow-up study of multiple sclerosis, cerebellar deficits resulting in difficulties with functional activities were found to occur in 33% of 259 patients and to be predictive of a worse outcome (Weinshenker et al. 1996; Weinshenker 1997) . Similar proportions of patients with MS were reported to have moderate tremor (Haddow et al. 1997) or ataxic symptoms (Alusi et al. 1999a) in other studies. A recent study of tremor in 100 patients with MS randomly selected from the Central Middlesex Hospital MS Unit register showed that tremor occurs in about half the MS population and is disabling in about one sixth (Alusi et al. 1999b). Tremor therefore occurs more commonly than previous estimates suggest.

There may be several reasons for this under-estimation of tremor in MS. Firstly, the incidence and prevalence of MDMS are difficult to estimate since it is often difficult

to distinguish intention tremor from the motor dysfunction due to serial dysmetria. In addition, the relapsing and remitting nature of the disease process in the early stages of MS results in transient neurological signs that make it difficult to assess the full extent of the problem.

1.2.1 Types of MDMS

There is considerable controversy surrounding the precise definition and identification of the different components of the disorders of movement which are commonly seen in patients with MS and which are produced by cerebellar disease.

Until very recently there have been no detailed prospective studies of MDMS determining the incidence of the various types of MDs. However Alusi et al (Alusi et al. 1999b) recently studied 100 patients with MDMS and showed that tremor affected the upper limbs in 55%, the lower limbs in 11%, the head (titubation) in 7% and the body (truncal ataxia) in 5%. However, it was not clear from data provided what percentage of patients had tremor affecting both the upper limbs and trunk which seemed surprising as the majority of patients referred for assessment of their MD (movement disorder) in the present study commonly presented with titubation of the head and truncal ataxia.

Most textbooks still rely on Gordon Holmes's descriptions (Holmes 1917), which highlighted that in cerebellar disorders there are, in addition to tremor, decomposition of voluntary movement, asynergia (failure of smooth co-ordination of the movement's component parts), dysmetria, and dysdiadochokinesia (inability to perform rapidly alternating movements) all occurring together. Clinical descriptions

do not distinguish between these different components (tremor, dysmetria and other ataxic features) but merely describe the whole disorder loosely under the term, ataxia.

It is very difficult to differentiate tremor, dysmetria and ataxia in clinical practice (Alusi et al. 1999a). However according to the International Tremor Foundation 'Tremor Investigating Group' (TRIG)

> 'as long as the dominant feature of the movement disorder is rhythmicity, it should be labelled as tremor' (Deuschl et al. 1998).

In MS, tremor can affect the upper limbs, head and axial muscles (Compston 1986) and is

> 'present when the limb is at rest (it may subside if one can get the limb into complete repose), increases with the maintenance of posture and is markedly exaggerated by an attempted movement.' (Weiner and Lang 1989)

However, the disorders of movement observed during a voluntary movement of a limb of a patient with MS can not always be described as rhythmical but appear irregular, not patterned, uncoordinated and flailing. The name of this tremor syndrome has long been a matter of debate. The traditional terms, 'rubral' and 'midbrain' tremor have been used in the past but are now considered misleading because more and more lesions outside these classic locations are described with the same or similar phenomenology (Nakamura et al. 1993). Holmes (Holmes 1917) gave one of the first concise descriptions of 'rubral' tremor in 1917 and emphasised that patients who had this type of tremor exhibited tremor at rest. Holmes' tremor has been introduced (Deuschl et al. 1998) as a substitute for the misnomer 'rubral' tremor to avoid names that include topographic descriptions. It is important to note

however that patients with MS do not have tremor at rest and therefore do not have true Holmes' tremor (Alusi et al. 1999b) .

To overcome this confusion with nomenclature for the purposes of this study, it was therefore decided to refer to these dyskinetic movements in which tremor played a prominent but not a unique role, under the umbrella term of movement disorders. However it was apparent that not only were there difficulties in attempting to distinguish between tremor and associated ataxic components of a MDMS but there were also difficulties in classifying and grading the different types of tremor. Several studies have reported difficulties with scoring tremor (Bain et al. 1993; Bain et al. 1994; Bain 1999) . Bain describes a recent study (Bain et al 1993) in which he and three other neurologists with experience in the field of assessing disorders of movement rated 20 patients for upper limb tremor. They agreed on the definitions for rating different types of tremor between themselves beforehand. Despite this, there was poor agreement among the assessors concerning which of the patients had kinetic or intention tremor and even less agreement on the severity of these two components of tremor.

A working consensus for the classification and definition of tremor based on the assumption that different components of tremor can be separated by clinical observation has recently been reached (Deuschl et al. 1998) . This classification was based on that of the Tremor Investigation Group (TRIG) (Findley and Koller 1995) which was devised and adopted for this study in 1995. It favours the classification of tremor into rest and action varieties. Action tremor is any tremor that is produced by

voluntary contraction of muscle: it includes postural, isometric and kinetic tremor. The last of these includes intention tremor, the notion of which

'brings us to the murky waters of the concept "ataxia"' (Hallet 1986)

1.2.1 (i) Rest tremor

In MS true rest tremor (tremor which is present in a body part that is not voluntarily activated and that is completely supported against gravity) is not seen (Alusi et al. 1999b) .

1.2.1 (ii) Action tremors

Postural tremor

Postural tremor is present while voluntarily maintaining a position against gravity and can be present in the head, trunk and limbs. If postural tremor is severe it may be present on lying and may inaccurately be called rest tremor, because the patient is unable to relax completely. This type of tremor is referred to as titubation when it affects the head and trunk and it can be particularly striking when a patient is standing. A large amplitude 'wing beating' postural tremor that increases progressively on maintained posture has been well described (Hallet et al. 1985; Sabra and Hallet 1984) , thus the postural component must be evaluated with the arms extended and arms flexed (Nguyen and Degos 1993) .

Alusi *et al* recently reported that different types of postural tremor were encountered in their study of 100 patients with MDMS. These were a) distal, some of which resembled essential tremor; b) proximal high amplitude; c) combined proximal and distal; d) dystonia-associated. However the operational definitions for assessing these different types of postural tremor were not provided in the report of the preliminary findings from this study.

Kinetic tremor

Kinetic tremors occur during any voluntary movement. Intention tremor is seen when tremor amplitude increases during visually guided movements towards a target. This type of tremor is commonly seen in patients with MS and has a tendency to worsen with increasing precision requirements and is influenced by hypotonia (Sabra and Hallet 1984). Cerebellar tremor is often used synonymously with intention tremor although various other clinical expressions of intention tremor have been described recently. These include 'hyperkinetic tremor' (Findley and Gresty 1981) which combines proximal postural and kinetic components (Alusi et al. 1999b) , also called 'severe postural cerebellar tremor' by several authors (Hallet 1986; Nguyen and Degos 1993; Sabra and Hallet 1984) . These terms are not yet commonly used in clinical practice and although the description of hyperkinetic tremor better describes the flailing movement that is seen throughout a voluntary movement performed by a person with MDMS it is not clear how one goes about assessing such a movement. There is no doubt that this type of uncontrolled movement disorder combining postural and kinetic components is common in patients with MS as was shown in

Alusi *et als* study in which the commonest components were 'hyperkinetic' and distal postural tremor.

There has been a great deal of confusion in the past regarding the use of the term 'intention tremor' as it has been used in reference to tremors on contemplating, initiating, performing or completing a movement and is therefore very ambiguous. Indeed Gilman believes that

> 'Ataxic or intention tremors are the oscillations of the extremity which occur during movements. In current terminology, both of these types should be labelled "kinetic tremors". The term "intention tremor" should be avoided because of the frequent misinterpretation of its meaning.' (Gilman 1981)

The classification adopted for this study continued to use the term 'intention tremor' because it is common practice amongst clinicians. However, intention tremor was combined with kinetic tremors (kinetic/intention), because there are practical difficulties with trying to assess the component parts of a movement and it is therefore better to avoid this difficulty and to make an overall assessment of the kinetic movement of the limb as it moves towards a target. It must be stressed that when assessing kinetic/intention tremor in this study the goal directed movement was observed from start to finish rather than limiting the assessment to the end of the movement as has been done in other studies (Alusi et al. 1999b) .

1.2.1 (iii) Goal-related tremor

Goal related tremor is the appearance of kinetic tremor during the performance of highly skilled, goal-specific movements. Kinetic tremor in MS persists or worsens with goal-directed movement and it is associated with dysmetria (Hallet 1986) .

Analysing a goal directed movement is complex. There are several problems that can induce an oscillation in the terminal component of a goal directed movement, namely true intention tremor, serial dysmetria, low frequency sway movements resulting from proximal postural instability and postural tremor that has been inhibited by motion.

1.2.2 Pathophysiology of MDMS

The pathological basis for the MDMS is unclear (Bain 1999) . In MS the disease process affecting the cerebellum and its connections is usually too diffuse to allow accurate localization of the lesions which underlie the tremor. The source of tremor is most likely to be demyelination along the pathway from the dentate nucleus of the cerebellum to the ventro-intermediate nucleus in the thalamus (VIM), rather than demyelination in the cerebellum itself (Holmes 1904). A facilitatory loop exists whereby sensory information is relayed from the contralateral sensory-motor cortex via the pons to the cerebellum. The output then projects via the thalamus to the motor cortex. Movement disorders are a result of disinhibition of this loop (Goldman and Kelly 1995) .

There have been no *post mortem* studies linking the tremor of multiple sclerosis to a discrete lesion but clinical-pathological correlation has demonstrated that the lesion responsible for intention tremor in MS is almost certainly in the superior cerebellar peduncle and that lesions of the red nucleus are not relevant (Hallet 1998). These lesions in the superior cerebellar peduncle may lead to secondary changes in the function of the VIM which may act as a pacemaker and drive the tremor

(Narabayashi 1992). Narabayashi's study of the recordings from the VIM nucleus of the contralateral thalamus have shown abnormal neuronal activity leading to the possible identification of tremor-generating cells (Narabayashi 1992). It is believed that a destructive lesion (thalamotomy) or stimulation (DBS) of cells in the V.I.M. nucleus will suppress tremor either by interrupting the aberrant pathway or by destroying tremor generating cells or via both mechanisms. Recently other areas of the ventral nuclear group in the thalamus such as the ventral oralis posterior (VOP) have also been suggested to be important in the genesis of tremor (Lenz et al. 1994). Although the studies by Narabayashi and Lenz were carried out in patients with Parkinson's disease, their results could be relevant to patients with MDMS.

1.3 The Management of MDMS

Tremor is an involuntary rhythmic oscillatory movement of a body part and is one of the most disabling and distressing symptoms experienced by people with multiple sclerosis (Tranchant et al. 1995). There are few clinical syndromes therapeutically more frustrating for the neurologist than patients with MDMS who present with a combination of proximal upper limb tremor, titubation of the head and violent shaking of the trunk on attempting a change in posture or a simple goal-related activity (Matthews 1988).

Although there are a number of methods of treatment documented, few result in any significant benefit.

1.3.1 Physiotherapy and Occupational Therapy

Rehabilitation is aimed primarily at improving the ability to perform functional tasks through reduction of and compensation for tremor. Direct treatment of tremor involves techniques such as joint approximation and compression, viscous damping and bracing of the limb, facilitation and re-education of posture and movement and weights (Barlow and Schwab 1971; Chase et al. 1965; Hasler 1981; Howison et al. 1978; Morgan et al. 1999; Sutherland 1982) . The use of weights has not found widespread support because relatively high loads are required for control of tremor and this can exacerbate fatigue and weakness. In addition, compensatory approaches are also used by therapists (Ayres 1963; Rood 1962; Voss 1972) . These include the provision of aids and equipment such as weighted utensils or the 'Neater Eater' a damped eating device manufactured by Michaelis Engineering, (Buxton, UK), alterations to the patient's postural support, for example using a chair with a winged headrest for postural head tremor, adapting the patient's environment and advising on different ways of carrying out activities. Although these methods of treatment are documented there has been little evidence until recently to suggest that they result in any significant benefit. Jones's study (Jones et al. 1996) recently demonstrated that adopting a multi-disciplinary approach to the above strategies could have a beneficial impact on disability and handicap in patients with MS.

1.3.2 Drug management

No established pharmacological therapy exists for cerebellar tremor. No single pharmacological pathway exists as multiple neurotransmitter systems are involved (Wasielewski et al. 1998). Current options for medical treatment have been described

as 'disappointing' (Poser et al. 1983), 'of no benefit' (Nguyen et al. 1996), 'ineffective' (Wasielewski et al. 1998) and 'of limited success' (Rice et al. 1997). Unfortunately for this group of patients the benefit of the medication is usually outweighed by the side effects and the general opinion is that no drug can produce a worthwhile improvement. The medications listed in table 1-2 have been tested on small numbers of patients with MDMS but with variable success.

Four of the 15 patients who underwent surgery in the present study had been tried on different medications for tremor. The medications most commonly prescribed were primodone, propranolol, and ondansetron. None of the patients were taking any medication to control their movement disorders at the time of operation.

Table 1. 2: Studies evaluating drug therapies

Study	N=	Drug	Dosage (/day)	Effect
(Sechi et al. 1989)	7	carbamazepine	400-600 mg	All patients improved on clinical rating scales and accelerometry, titubation improved but dysmetria persisted
(Koller 1984)	6	propranolol	120 mg	No benefit
(Elbe and Koller 1990)	6	primidone	50-250mg	Ineffective
(Hallet et al. 1985)	6	isoniazid	1200 mg	Effective for severe postural tremor, no effect on intention tremor or functional improvement
(Koller 1984)	3	isoniazid		No effect
(Aisen et al. 1991)	6	glutethimide	750-1250 mg	Functional benefit in 5 patients, side-effect of persistent sedation in all patients, persistence of dysmetria
(Trelles et al. 1984)	2	clonazepam	9-15 mg	Abolished intention tremor
(Clifford 1983)	8	tetrahydrocannabinol	5-15 mg	Beneficial effect in 2 patients
(Rice et al. 1997)	16	ondansetron	8 mg	Significant benefit on spiral copying and 9 hole peg test. Subjective response in 9 patients- 'better'

1.3.3 Surgical treatments

1.3.3 (i) Thalamotomy

Irving Cooper first described thalamotomy in patients with MDMS more than three decades ago. Thalamotomy is a neurodestructive procedure where brain tissue is ablated either by thermocoagulation, cooling or chemical means. Haddow and coauthors (Haddow et al. 1997) reviewed 14 articles published between 1960 and 1992, describing thalamotomy for tremor in patients with MS. The total number of patients amounted to 234. The results from this review suggests that in selected patients with MS 65–90% of patients showed immediate symptomatic benefit from thalamotomy and 70% were reported to still be improved at one year (Goldman and Kelly 1992; Hitchcock et al. 1987; Speelman and Van Manen 1984). However functional improvement of the relevant arm is estimated to óccur in only 25 – 47% of patients (Goldman and Kelly 1992; Haddow et al. 1997; Hitchcock et al. 1987; Speelman and Van Manen 1984) .

The benefit in functional ability due to the resolution of the tremor after thalamotomy at 12 months was disappointing and only addressed in a small number of papers (Goldman and Kelly 1992; Hauptvogel et al. 1975; Hitchcock et al. 1987; Speelman and Van Manen 1984; Whittle and Haddow 1995) . Only one series on 11 patients provided detailed post-operative data on the functional results of thalamotomy (Speelman and Van Manen 1984) .

Despite the relief of tremor afforded by thalamotomy in the short term, the authors of Haddow's review concluded that they had several reservations about the use of this procedure in patients with MS. These included moderation of benefit due to the

remaining ataxia, immediate post-operative side-effects and a possible negative influence on the rate of progression of the disease process.

The morbidity was high with percentages between 18% to 57% of patients experiencing permanent adverse effects (Goldman and Kelly 1992; Speelman and Van Manen 1984) . The most often reported complications of thalamotomy are worsening of gait, hemiparesis and dysarthria. In addition, epilepsy, sensory disturbances, dysphagia, transient bladder disturbances, depression, confusion, lethargy and somnolence have also been, albeit rarely, described (Barnett et al. 1992; Haddow et al. 1997; Shazadi et al. 1996; Speelman and Van Manen 1984) . The side effects associated with thalamotomy for MDMS are more severe than those observed in Parkinsonian or essential tremors (Benabid et al. 1996). In his series of 11 patients, Speelman (Speelman and Van Manen 1984) reported permanent hemiparesis in four cases, and one died of aspiration pneumonia 3 weeks after surgery. Barnett et al (Barnett et al. 1992) recently observed permanent hemiparesis in two of six patients. So far, one patient has been reported with a relapse of the MS, probably in relation to the surgery (Goldman and Kelly 1992). The site of the thalamotomy has to be selected according to the somatotrophic distribution inside the VIM nucleus and the size of the lesion has to be larger when the tremor involves the proximal muscles (Hirai et al. 1983).

There are inadequate data on the post-operative course of individual patients and the length of follow-up in many of the series reported in the literature. Long term follow up after thalamotomy was reported at 18 months (Speelman and Van Manen 1984), two years (Goldman and Kelly 1992; Hitchcock et al. 1987), and three years (Arsalo

et al. 1973). However, little useful information can be derived from the last study by Arsalo *et al* which has the longest follow up of MS patients after thalamotomy as there were major methodological weaknesses in the study. No validated scales were used, tremor type was not specified, tremor severity was not objectively quantified and there was no measurement of the ability to perform tasks of function using the upper limb.

Long term outcome after thalamotomy is an important issue since it is likely that the profiles of MS patients chosen for either thalamotomy or thalamic DBS would be similar. The longer term outcome of MS patients who had been treated with thalamotomy in the Department of Clinical Neurosciences (DCN) between 1989 – 1994 was evaluated for effect on tremor resolution and disability, with a minimum of three year follow-up (Hooper and Whittle 1998).

All 10 patients had a form of cerebellar tremor which had been distinguished clinically into either a 'rubral' tremor characterized by severe postural tremor affecting the head, trunk and upper limbs, with a superimposed kinetic/intention component that was present during volitional limb movements; or an isolated kinetic/intention tremor. All patients were severely disabled and had no functional use of their affected upper limbs. After computerised tomography (CT) image-guided ventrolateral thalamotomy, brachial tremor was reduced in 9 of 10 patients immediately after the operation (Whittle and Haddow 1995). None of the patients with severe 'rubral' tremor had complete abolition of their movement disorder, and although it was reduced in most patients they remained disabled. This was often partly due to the unmasking or persistence of cerebellar disease. At one year follow-

up only three patients, who had the best preoperative Barthel scores, were functionally improved (cases 4, 5 and 10). At final review, a median of 56 months after operation, only six patients remained alive, and one (patient 10) remained improved in their ability to carry out activities of daily living (Appendix1).

This review of the patients who underwent thalamotomy for MDMS had some important implications. First, the results strongly suggested that in many patients the onset of severe disorders of movement was followed by a progressive functional decline, and even death, due to the MS. Secondly, although stereotactic surgery may have some temporary functional benefits, except in the occasional case the surgery is unlikely to have a major longstanding beneficial impact, predominantly because of additional CNS damage due to the MS. Thirdly, adequate evaluation of thalamic DBS in MS patients with movement disorders will require long term follow up not only in view of the poor long term outcome of these patients who have undergone thalamotomy in the past but also because there are important clinical, management and health economic implications associated with its use (Geny et al. 1996; Whittle et al. 1998).

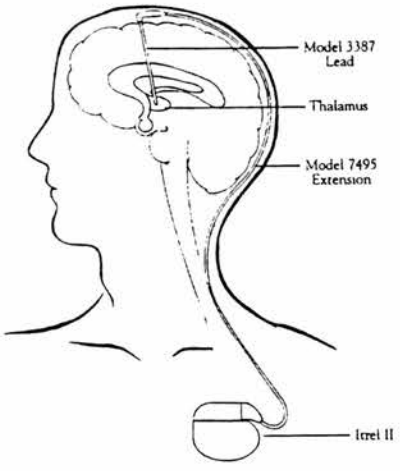
1.3.3 (ii) Thalamic deep brain stimulation

Thalamic deep brain stimulation involves stereotactic surgery to implant an electrode in the ventrolateral nuclear complex of the thalamus and implantation of a pulse generator and connecting lead to generate electrical impulses which are delivered to the electrode. The technique of thalamic deep brain stimulation (DBS) was first described in 1980 by Brice and McLellan (Brice and McLellan 1980) for movement

disorders which were due to multiple sclerosis. Since that time there have been substantial technical advances in DBS hardware and brain imaging. Thalamic DBS, which is a less destructive surgical method than thalamotomy, is an established treatment for Parkinson's disease (Benabid et al. 1996). One of the cogent reasons for the limitation of thalamotomy is the reluctance to cause additional permanent lesion of the CNS. Chronic DBS offers the advantage of being non-destructive, reversible and adjustable if necessary. Another advantage is that with bilateral DBS procedures, there are significantly fewer complications than with bilateral thalamotomy (Benabid et al. 1991).

Components of the Thalamic Stimulation system

Figure 1-4:Thalamic stimulation system components



The Medtronic thalamic stimulation system (Figure 1-4) consists of three implanted components: a stimulation lead (DBS electrode), an extension wire and an implantable pulse generator (IPG).

The stimulation lead consists of four insulated wires connected to four electrical contacts, or electrodes. The stimulation lead is implanted in the ventrolateral thalamus and it is connected to an extension wire that connects distally to the IPG. The IPG is commonly implanted in the chest wall in the subclavicular region. The IPG is a small sealed metal container with a 3.7-volt battery and the electronics for the thalamic stimulation system.

The IPG is programmed percutaneously using a computer to set the appropriate intensity, pulse duration and rate of stimulation. The computer programs the IPG through a programming head placed on the skin over the IPG. The goal is to maximize suppression of the tremor with minimal or no side effects. Patients require their own unique parameters of stimulation to suppress tremor. In Geny's series of 13 patients with MS treated with thalamic stimulation they showed that the possibility of modifying the electrical variables and the site of stimulation after surgery was crucial for obtaining optimum results on tremor (Geny et al. 1996).

A secondary goal of programming is to prolong battery life. Optimal programming of the thalamic system of stimulation is used to achieve these goals.

Relatively little information exists on the value of this treatment in MDMS, although one study suggested good results in 69% of patients (Geny et al. 1996). There have now been 7 papers on a total of 48 patients which have described the relative merits

of thalamic DBS (Benabid et al. 1996; Brice and McLellan 1980; Geny et al. 1996; Nguyen and Degos 1993; Schuurman et al. 2000; Siegfried 1993; Taha et al. 1999) and the associated problems encountered with the procedure (Whittle et al. 1998). Schuurman's study (Schuurman et al. 2000) of 68 patients (45 with Parkinson's disease, 13 with essential tremor and 10 with MS) randomly assigned to undergo thalamotomy or thalamic DBS recently claimed that 'there was a significant difference in the incidence of adverse effects' between the two groups with DBS being safer. However this claim should be regarded with some caution as one patient with Parkinson's disease in the thalamic stimulation group died during the operation after an intracerebral haemorrhage. Also, 16 of the 34 patients in the thalamotomy group had persisting complications at six months post-operatively. This rate is higher than the rate in most published series for permanent complications after thalamotomy in Parkinson's disease, essential tremor (Jankovic et al. 1995) and MS (Haddow et al. 1997); however it was a prospective study.

Even though thalamic DBS is more flexible than thalamotomy in allowing the stimulation parameters to be adjusted, if systemic functional decline due to the MS parallels that previously described (Geny et al. 1996) and seen in the thalamotomy cohort reviewed as part of this study (Hooper and Whittle 1998) thalamic DBS will only have temporary beneficial effects.

There are disadvantages associated with thalamic DBS and these include higher costs, limits imposed by the hardware, the need for replacement of the batteries and the natural resistance to the implantation of a foreign body. With regard to the important question of long term tolerance, two studies have reported equipment

related complications (Benabid et al. 1996; Schuurman et al. 2000). Three patients in Benabid *et al's* study had late scalp infections necessitating removal of the DBS electrodes and in one patient in Schuurman *et al's* study the pulse generator site became infected and had to be replaced after antibiotic therapy.

It is agreed that there is a need for further prospective studies of thalamic DBS (Krauss and Mundinger 1996; Speelman et al. 1998; Whittle et al. 1998) to determine not only the long term efficacy of this novel treatment and its potential advantages compared with stereotactic thalamotomy but also to avoid inappropriate application and unnecessary morbidity. The considerable cost implications of thalamic DBS also merit consideration to prevent wastage of funds.

1.4 The Effectiveness of Stereotactic Surgery for MDMS

1.4.1 Measurement of movement disorders in MS

Previous studies evaluating the effect of stereotactic thalamic surgery for MDMS were largely observational studies. When measurement of the movement disorder was undertaken it was performed using tremor rating scales which had not been validated for the purposes of the studies. No laboratory based measures have been used to measure the outcome after surgery in patients with MDMS.

1.4.1 (i) Observational studies

Haddow's review of the literature on thalamotomy (Haddow et al. 1997) highlights some of the weaknesses associated with the design of past studies involving patients with MDMS.

The diagnosis of MS was made purely on general clinical examination and signs in all but two of the studies: one study (Speelman and Van Manen 1984) used criteria defined by McDonald and Halliday (McDonald and Halliday 1977) and the other study (Hauptvogel et al. 1975) used Poser's criteria (Poser et al. 1983) to confirm a specific diagnosis of MS.

Prior research has been based on small numbers of patients with MDMS who were incidentally sampled for the studies. This introduced an element of bias to the studies as there was no form of randomisation performed. The results which were reported were concerned with comparatively small samples of patients with MS who were grouped along with many patients having surgery for other neurological conditions such as Parkinson's disease and essential tremor. The majority of studies were therefore not designed to address specific problems occurring in the MS subgroup and development of valid and sensitive scales to assess the outcome of surgical treatments in this cohort was not a priority.

Few of the studies that have addressed thalamotomy for MDMS have had rigorous evaluations of the patient cohorts preoperatively and postoperatively: postoperative follow up was poorly defined and only 3 articles had rigid long term follow-up times (Hitchcock et al. 1987; Speelman and Van Manen 1984; Van Manen 1974). The

operative procedures varied: the targets for lesioning were variable. Usually the ventrolateral nuclear complex (VL) was targeted (Goldman and Kelly 1992; Speelman and Van Manen 1984; Whittle and Haddow 1995) without any more specific details being provided; sometimes in isolated studies a specific area of this nucleus was nominated. Methods of physiological target localisation were varied and included exploratory brain stimulation with clinical monitoring in the conscious patient (Arsalo et al. 1973; Whittle and Haddow 1995) and microelectrode recordings (Goldman and Kelly 1992). The method of creating the lesion varied and was most commonly by thermocoagulation (Goldman and Kelly 1992; Whittle and Haddow 1995). It was also not clear whether confounding variables such as drugs prescribed for tremor which may have had an effect were controlled for in past studies. This issue of confounding variables was not discussed in any of the studies and was therefore probably not given any consideration.

As a consequence it is difficult to draw any meaningful conclusions from past studies as statistical testing was probably invalid due to the limitations and weaknesses discussed. The claim that 70% of MS patients still had reduced tremor 12 months after surgery (Haddow et al. 1997) must therefore be regarded with a great deal of caution.

1.4.1 (ii) Subjective rating scales

> 'The quality and utility of much of the literature concerning the surgical treatment of tremor in patients with MS is suboptimal' (Haddow et al. 1997).

The most common method of assessing the response of tremor to thalamotomy and other different therapies for MDMS in the past has been the re-evaluation scoring of

tremor and disability scales (Goldman and Kelly 1992; Hitchcock et al. 1987; Speelman and Van Manen 1984; Whittle and Haddow 1995). However, this has been done in a variable way using a wide range of poorly defined, *ad hoc* scales, which have often not been thoroughly evaluated for reliability, validity and sensitivity.

Hitchcock's study (Hitchcock et al. 1987) of 47 patients who underwent thalamotomy for movement disorders, between 1979 and 1984, included 30 patients with MS and used what they described as "a simple grading of symptomatic improvement in terms of 'cured', 'improved' or 'unchanged'. Arsalo's study (Arsalo et al. 1973) involving 26 patients treated with thalamotomy for intention tremor used a measurement scale which was equally crude: a 'good' outcome meant no remaining tremor in the hand for which thalamotomy had been performed when the patient was discharged from hospital, a 'fair' outcome meant that some tremor could still be seen; and a poor outcome meant that the effect of thalamotomy on tremor was minimal.

There are major problems with the use of these scales as they are highly subjective requiring the examiner to make a personal judgement as to what they regarded 'improved' and 'minimal' to mean. There were no operational definitions given for using the scales, and the authors did not define what was being measured or differentiate between the different types of tremor. These scales were consequently not shown to be valid or reliable and the results and conclusions of these studies must be regarded with caution.

Speelman's study (Speelman and Van Manen 1984) was the only study of thalamotomy for MDMS which provided detailed pre and post-operative data, and presented results in such a way that it was possible to relate changes in disability scores and functional status scores to specific patients. Speelman designed a scale for this study to rate the severity of tremor in the 11 patients with MS after thalamotomy. It was an ordinal 0 – 3 point scale where 0 = no intention tremor, +1 = slight intention tremor: minimal impairment of arm, +2 = moderate intention tremor: ability to keep the hand within 15cm of an intended object, +3 = severe intention tremor: inability to keep the hand within a distance of 15cm of the intended object. It was claimed to be measuring the severity of intention tremor but instead was assessing the patient's ability to voluntarily maintain a position against gravity which according to the recent classification of tremor (Deuschl et al. 1998) based on the work of the Tremor Invesigation Group is the definition of postural tremor. Another major weakness of Speelman's study was that no attempt was made by the author to establish the psychometric properties of the scale.

Fahn gave a detailed account of his scale in a book called 'Parkinson's Disease and Movement Disorders' (Fahn et al. 1988). Since then it has been widely used in its published form in studies assessing tremor severity in Parkinson's disease, essential tremor (Hariz et al. 1998; Hubble et al. 1996; Schuurman et al. 2000) and cerebellar outflow lesions (Krauss et al. 1994). It has also been used in a modified form by Benabid et al (Benabid et al. 1991; Benabid et al. 1996). Despite the continued use internationally of Fahn's Tremor-Rating Scale there has been no validatory work carried out to assess the reliability, validity or sensitivity of the use of the Fahn's

Tremor Rating Scale (FTRS) in any group of patients. It has been described by Goldman and Kelly (Goldman and Kelly 1992) as an 'established scale' presumably because of its widespread use and not because it has been shown to be psychometrically sound. They used the FTRS to explore the symptomatic impact of thalamotomy for tremor in 14 patients with movement disorders, five of whom had intention tremor due to MS.

Fahn's scale differed from other scales in that it was the first tremor rating scale to be used that measured the different components of tremor (rest, postural, action/intention) and also the severity of tremor in different areas of the body (head, trunk, upper limbs and lower limbs). It was a five level (0 – 4 point) scale which quantified tremor according to the magnitude of the tremor amplitude and was rated as 0 = none, 1 = slight (amplitude <0.5cm), 2 = moderate (amplitude 0.5 – 1cm), 3 = marked (amplitude 1 – 2cm) or 4 = severe (amplitude >2cm).

No special tools were required other than a pencil, paper and two cups to hold water. In addition a task-specific quantification involving handwriting, drawing and volumetric tasks, functional disability were also included. The scale also provided definitions to allow subjective global assessments of tremor, including subjective comparisons by the patient for evaluating the effectiveness of treatment and variations in severity of tremor over time.

The disability scale in FTRS has been used independently in different studies to assess and quantify disability. Krauss *et al* (Krauss et al. 1994) used it when reporting the long term results of stereotactic surgery in 35 patients with severe upper

limb tremor due to traumatic brain injury. They showed that functional disability was reduced from a mean value of 57% of maximum disability to 37% over the longer term ($p < 0.001$). Goldman and Kelly (Goldman and Kelly 1992) also used the disability scale in a slightly modified form (omitting assessment of speech) to evaluate disability in nine patients (three patients after infarction, three patients after trauma and three patients with MS) who had undergone thalamotomy for disorders of movement of the upper limb. They calculated the mean disability scores and separated out the disability scores by aetiology. The only subgroup to attain a statistically significant ($p = 0.02$) postoperative reduction in disability score was the post-infarction patient group; however, the MS patients and trauma patients tended towards improved disability.

Comparing changes in mean disability scores as was performed in the above two studies is hazardous as Fahn's Functional Scale is an ordinal scale which means that a difference of one point is clearly not equivalent throughout the scale. It provides a rank ordering of the patient's ability to perform the functional tasks specified in the scale and therefore comparing mean scores is potentially misleading and should be avoided.

Some of the more recent studies evaluating thalamic DBS have made some attempt to use scales that are more objective and quantify the severity of tremor, as can be seen from Table 1-3:

Reference	N	Tremor Grading	Dysfunction Grading	Follow-up	Other outcomes
Brice (1980)	3	–	–	6 months	–
Benabid (1993), (1996)	4	Reference to Fahn's TRS in methods BUT (0-4) scale, 0= no benefit, 4 = complete disappearance of tremor Scale not based on measurement of tremor amplitude and therefore had been modified	–	unclear	Video 5 point improvement scale 0=no benefit,4=complete disappearance of tremor
Nguyen & Degos (1993)	4	Speelman' s tremor scale (0-3) 0=no intention tremor, 3=severe intention tremor: inability to keep the hand within a distance of 15cm of the intended target	Speelman's FS (0-4) 0=no handicap, 4= no control of arm	Mean 17mths	–
Seigfried & Lippitz (1994)	9	–	–	unclear	'perfectly controlled without side effects'
Geny (1996)	13	Geny's tremor severity scale (0-4) 0=no tremor, 4=amplitude>10cm	Modified Speelman's FS (0-5) 0=no handicap,5=no control of arm, intermediate state added that corresponds to throwing/catching a ball, using an object	8-26mths (median 12mths)	Video Clinical exam
Whittle (1998)	8	*Modified FTRS (0-4) 0=no tremor, 4=severe tremor, amplitude>10cm	Fahn's FS, Jebsen THF, self-care section of FIM, BI	Preliminary results (12 mth data to be presented later)	Video, EDSS Neuropsychological test, clinical exam, Measures of handicap,QOL and patient perception
Schuurman (2000)	5	Speelman's modified tremor severity scale (0-4)	Frenchay Activities Index-15 ADL measured on a 0-4 pt scale	2 years (6 mth data used in analysis)	No. of adverse effects, EDSS, patient's assessment of outcome

*=Scale validated for use with MS patients

Benabid *et al* claimed that it was FTRS which was being used in their studies (Benabid et al. 1991; Benabid et al. 1993; Benabid et al. 1996) and referred to Fahn's published methods. However the scale that was used to assess the severity of tremor was not the scale proposed by Fahn as it was not based on the assessment of the amplitude of tremor. It was a 5 point scale but it used different operational definitions to quantify the tremor (4 = complete disappearance of tremor in all circumstances; 3 = reappearance of a slight tremor in rare circumstances, for instance under stress; 2 = moderate benefit; 1 = slight benefit without real improvement in daily life; 0 = no benefit at all or worsening of tremor). No mention of this change to Fahn's scale was made in the paper.

Geny's *et al*' s study (Geny et al. 1996) evaluated the effect of thalamic DBS on 13 patients with MS. The authors devised a scale that was similar to FTRS in that it quantified tremor according to the magnitude of the tremor amplitude. The scale was designed specifically for patients with MDMS and defined the tremor amplitude from 0 – 10cm: 0 = no tremor; 1 = maximal amplitude <1cm; 2 = amplitude 1 – 5cm; 2 = amplitude 5 – 10cm; 3 = amplitude >10cm.

Fahn's scale was designed predominately for use with Parkinson's, essential tremor (ET) and cerebellar outflow patients and the tremor amplitude ranged from 0 – 2cm. Geny's scale which was designed specifically for patients with MDMS defined the tremor amplitude from 0 – 10cm. Geny *et al* also used a modified form of Speelman's functional scale to which an intermediate state was added that corresponded to the capability of easily catching an object. Although the scales were devised for the study they were not validated before being used. They have

subsequently been used in a recent comparative study of thalamotomy and thalamic DBS in Parkinson's, essential tremor and MS patients (Schuurman et al. 2000). Schuurman *et al* in their study used what was referred to as the 'Modified Tremor Scale' and quoted Speelman's article as the source of the reference for the scale. However the tremor rating scale used in Schuurman's study is a 0 – 4 point scale rather than a 0 – 3 point scale originally described by Speelman. We can only assume that Schuurman *et al* therefore modified the scale for the study although no reference of this alteration to Speelman's tremor scale is given in the paper. Nguyen (Nguyen and Degos 1993) also used Speelman's Functional Scale in his study evaluating the effect of thalamic DBS on proximal upper limb tremor in 4 patients with MS. Despite the continued use of these scales in patients with MDMS no attempt has been made to validate their use on this group of patients.

Design of rating scales for tremor is in a process of evolution but, at present, no validated scale is available for assessing movement disorders in multiple sclerosis (Haddow et al. 1997). This is in contrast to both essential tremor and Parkinsonian tremor for which there are subjective scales such as the Webster Rating Scale (Webster 1968) and the Unified Parkinson's Disease Rating Scale (version 3.0) (Fahn and Elton 1987) for measuring movement disorders. Presumably these diseases have been the focus for the development of tremor rating scales in the past because treatments exist that reduce impairment such as tremor and bradykinesia. Unfortunately most of these scales tend to mix impairment with disability, using the disability to rate the severity of the impairment, and have poor operational definitions. This is illustrated in the Unified Parkinson's Disease Rating Scale where

a score of 3 indicates marked tremor, which interferes with many activities, and a score of 4 indicates severe tremor, which interferes with most activities. Both the Webster Rating Scale and the Unified Parkinson's disease Rating Scale have been widely used but there have not been any formal studies of reliability performed on either scale. As Elbe and Koller remark in their book on tremor

> 'Rating scales are imprecise and subjective. Most have evolved *ad hoc* from epidemiological and therapeutic studies, and none have received universal acceptance or validation.' (Elbe and Koller 1990)

The lack of a validated tremor rating scale presented a major problem for this present study as in order to critically evaluate the effect of thalamic DBS on MDMS measurement scales were required that had known validity, reliability and responsiveness.

Handicap and disability are important to patients and those who treat them and look after them, yet these areas have been neglected in previous clinical trials. Instead the focus has often been on measuring the amplitude of the tremor and its severity and too much emphasis has been placed on professionals' opinion of the outcome of treatment rather than that of the patient. This may reflect the bias of the professionals as well as difficulty in the satisfactory assessment of outcome using currently available scales of function, disability and handicap. Schuurman *et al's* recent study (Schuurman et al. 2000) which was a randomised comparison of DBS and thalamotomy which included 5 patients with MDMS in each group is one of the few studies that has focused on this issue, using functional status as a primary outcome

rather than symptoms of the disease. Furthermore, in no prospective study of patients with MDMS has the influence of tremor on overall disability, handicap and quality of life or the patient's perception of changed ability been measured.

1.4.2 Cost-benefit analysis

There are health economic implications associated with thalamic DBS. These arise from assessment, purchase (£7,602 per set) and implanting of the thalamic DBS; follow-up; comprehensive post-operative rehabilitation requirements in that patients need intensive physiotherapy and occupational therapy to relearn use of the target upper limb; and staff costs for support. Patients also need to be monitored for any adverse side effects relating to the stimulation and at some stage the IPG battery will need to be replaced. The cost involved with the purchase of the equipment alone is an obstacle for the use of thalamic stimulation as a regular treatment in some economically deprived countries. No study has addressed the cost-benefit of thalamic DBS although it had been stated recently that this was required (Speelman et al. 1998; Whittle et al. 1998) .

1.5 Challenges in the Measurement and Treatment of MDMS

1.5.1 Validation and use of tremor rating scale and upper limb function test

One of the most important aspects at the beginning of the study was to devise and validate a series of tests to enable prospective and objective documentation of the

clinical and disability status of patients with disorders of movement who were referred for (potential) therapy using thalamic DBS.

Fahn's Tremor Rating Scale (FTRS) and the Jebsen Test of Hand Function (JTHF) were chosen for use in this study over other existing tremor rating scales and hand function tests because they appeared potentially capable of quantifying tremor severity and quantifying deficit in performance of hand function. It was necessary to make some minor modifications and omissions to the original FTRS and then to evaluate the psychometric properties of the amended scale (Modified FTRS) to enable it to be used in patients with disorders of movement due to MS.

The first aim of the study was to assess the applicability of the modified version of FTRS (MFTRS) in the measurement of the disorder of movement for reliability and validity. The JTHF had already been extensively evaluated with regard to reliability and validity in neurological patients presenting with intention tremor.

1.5.2 Evaluation of thalamic DBS

After reviewing the past studies it was evident that there was a lack of objective evidence supporting the use of thalamic DBS in MS. The second aim of this study was therefore to determine whether thalamic DBS (i) decreased tremor and (ii) improved hand function in the target upper limb in patients with MDMS.

The issue of sample size presented a major problem in the proposed study as the size of the sample was determined by the number of patients with MDMS who were easily accessible and willing to be considered for inclusion in the study. The ideal solution to overcome the problem of incidental sampling and of a sample population

that may not be representative of the population would have been a large, multi-centred randomised controlled trial. However this would not only have been enormously costly but it would also have been very difficult to organise and therefore was not practical. The study sample was intended to include a representative sample of patients with MDMS thus including patients with movement disorders which ranged in severity from mild to severe. This study was therefore a pragmatic study intended to provide a preliminary evaluation of the relative merits of thalamic DBS in MDMS.

The proposed study involved extensive clinical, functional and video assessments of patients before surgery and at 1, 3, 6 and 12 months after surgery which were performed by the researcher, independent of the operating surgeon, with the stimulator on and off. The assessment procedure involved the patient and his family in the decision process and emphasized the importance of clear realistic goals to be agreed. The two main primary outcome measures used for assessing tremor severity and upper limb performance were to be the modified Fahn's tremor rating scale and the Jebsen test of hand function.

In addition, the effect of thalamic DBS on overall cognitive function, disability, handicap, quality of life and the patients' perception of the outcome of the treatment were also to be evaluated. Specific scales of cognitive function (neuropsychological test), disability (self-care section of the FIM and BI), handicap (LHS, Handicap Questionnaire) and QOL (FSS, HAD, subjective global assessment of tremor-related disability in the MFTRS, patients' opinion of outcome questionnaire) were used for this purpose.

1.5.3 Health economic measurement of the 'cost-benefit' of thalamic DBS

The third aim of the study was to provide an estimate of the costs involved in the patients in whom thalamic DBS were implanted for MDMS and to establish whether it resulted in any economic benefit (savings in future care costs) in this cohort of patients. If it were possible to demonstrate that as a result of thalamic DBS there was a reduction in resource use in the longer term then the overall/additional cost of the intervention might be offset.

1.6 Summary of the Study Objectives

The purpose of the work presented here was to study the effectiveness of thalamic DBS in MS. However in order to do this a series of clinical tests had to be devised and validated at the beginning of the study. The main aims were therefore to:

(i) determine whether current scales devised for rating tremor in patients with Parkinson's disease and essential tremor were appropriate for evaluating MDMS.

(ii) devise and validate standardized tests for use with MDMS which could be adopted by other centres performing such surgery so that results could be reported consistently and comparisons made.

(iii) provide a preliminary evaluation of the relative merits of thalamic DBS and thalamotomy in the management of patients with tremor due to MS with an emphasis on examining outcome in terms of not only quantitative change in

tremor, but on changes in disability, handicap, quality of life and patient perception of effectiveness.

(iv) address the cost implications of thalamic DBS

1.7 Hypothesis

The hypotheses under investigation were:

1. That there would be a difference between the pre and post operative scores and scores when the DBS was on versus off in the target upper limb of tremor severity (MFTRS) and performance of functional tasks (number of subtests of the JTHF passed) in patients with MS as a result of thalamic DBS.

2. That there would be a change in the ability to perform self-care activities of daily living (FIM), overall disability (EDSS), handicap (LHS and handicap questionnaire), fatigue (FSS) and mood (HAD) in patients with MS as a result of thalamic DBS.

3. That there would be a change in tremor-related disability post-operatively as perceived by the patient and examiner as a result of thalamic DBS (global subjective assessment in MFTR).

4. That the patients' subjective opinion of the outcome of the operation would be positive.

5. That there would be a change in the patients' functional ability in relation to activities of daily living (self-care assessment of FIM and BI) and therefore a change in the home-care resources used post-operatively by patients with MS as a result of thalamic DBS.

CHAPTER 2

MEASUREMENT OF IMPAIRMENT, DISABILITY, HANDICAP AND ASPECTS OF QUALITY OF LIFE ASSOCIATED WITH MOVEMENT DISORDERS IN MULTIPLE SCLEROSIS

2.1 Introduction

Measurement is a key process both in research and clinical practice and is 'the use of a standard to quantify an observation' (Wade 1992). If the measurement procedure is poor, then the validity of the findings, and hence the usefulness of the study, will be severely limited (Polgar and Thomas 1991) .

As discussed in the previous chapter many of the past studies evaluating stereotactic surgery for movement disorders due to MS did not use measures with proven reliability or validity. The lack of a validated scale for measuring movement disorders due to MS presented a major problem for the present study. It was therefore first essential to consider whether current scales devised for rating movement disorders in other situations might be appropriate for evaluating movement disorders in patients with MS. It was also clear that if a suitable tremor rating scale existed, studies of reliability and validity would be required.

2.2 Basic Requirements of Measuring Instruments

2.2.1 Reliability, validity and sensitivity

> 'The adequacy of any measure is determined by its reliability and validity' (Polgar and Thomas 1991)

Reliability refers to the reproducibility of scores obtained from a measure. A measuring instrument or test should have *reliability* in that the instrument should give the same result consistently when used repeatedly or by different examiners. These aspects of reliability reflect the stability or dependability of the measurement process. Therefore when assessing reliability one is assessing a process as well as an instrument (Seaby and Torrance 1992).

Scoring systems containing clear operational definitions generally improve reliability compared to vague, intuitive or judgmental approaches to assessment.

Standardized procedures similarly contribute to reliable and valid measurement and may be defined as using specified test administration and scoring procedures under the same environmental conditions, with consistent directions (Johnston 1992).

According to Johanson (Johnston 1992) inter-examiner reliability is a prominent issue with rating scales because if trained individuals cannot agree, the assessment procedure is of doubtful objectivity and utility. The extent of agreement is therefore a function not only of the inherent qualities of the assessment scale but also of features of the setting and the characteristics of the examiners.

Many of the procedures know to reduce unreliability were used in this study. An existing scale (Fahn's Tremor Rating Scale) was carefully developed and modified for use with patients with MS (Modified Fahn's Tremor Rating Scale). The Modified Fahn's Tremor Rating Scale had explicit operational definitions: defined criteria; standardized decisions and definitions; and instructions and guidelines for examiners to establish the rules for rating severity of the movement disorder.

However reliability is a necessary but not a sufficient condition for good or valid measurement (Kerlinger 1986) . A test should also have *validity* in that it measures what it sets out to measure. Any valid test will by definition be reliable but it is frequently ignored. This might be due to the fact that validity is more difficult to assess than reliability and frequently involves extensive analysis of the degree of agreement between different measures.

Ebrahim (Ebrahim 1991) argues that medical thinking about validity is preoccupied with criterion or 'gold standard' validity which may be appropriate for measuring biological impairments but is not in the case of measuring disability, handicap and quality of life, where no 'gold standards' exist. Consequently experts in the field of measurement have developed a logical scheme for categorising types of validity. There are five primary types of validity: face, predictive, content, construct and criterion validity (Rothstein 1993).

The truly ideal scale, which probably does not exist, should in addition to having the properties of reliability and validity, be sensitive to detecting change. Many scales are insensitive to detecting change particularly at the higher levels of recovery

(ceiling effect) or the lower levels of recovery (floor effect). The scale should be able to detect clinically important change over time, be easily used and widely applicable. There is a profusion of tremor rating scales and disability scales, which go nowhere towards meeting this ideal.

2.2.2 Features of ordinal scales of measurement

There are certain rules which need to be adhered to when using ordinal scales such as rating scales if they are to be used soundly.

An ordinal scale, which rates severity of tremor on a 5 point 0 – 4 scale where 0 = no tremor and 4 = severe tremor, provides a rank order of a patient's severity of tremor. With ordinal scales, statements about ranks can be made eg. if patient A scores 4 on the tremor rating scale and patient B scores 2, it can be said that patient A has more severe tremor than patient B. We cannot however, make statements about the relative size of these differences (ie. claim that Patient A's tremor is twice as severe as patient B's tremor), because the difference between each pair of ordinal positions on the scale is not necessarily the same. Such a scale is non-linear and therefore provides a non-quantifiable measure of severity of tremor (Oyster et al. 1987) which is not well suited to parametric statistical analysis. As noted above explicit operational definitions concerning each rank order on the scale help to ensure reliability.

2.3 Measurement of MDMS- Methods for Assessing Impairment

2.3.1 Kurtzke's Functional Systems (FS) and the Expanded Disability Status Scale (EDSS)

In 1955, Kurtzke proposed a scale for rating neurological impairment in MS. Between 1955 and 1983 the initial version was improved several times by Kurtzke. The 1983 version currently used is based on a two-phase procedure. First, eight neurological functions (pyramidal, cerebellar, brainstem, sensory, bladder and bowel, visual, cerebral and other) are assessed by standard neurological examination, where all save the last are graded from zero (normal) to maximal impairment (grade 5 or 6). The last category 'other functions' is dichotomous, with 0 = no other dysfunctions present and 1 = any other dysfunctions present. Secondly the overall disability is measured on the Expanded Disability Status Scale (EDSS). The EDSS is based on the eight measures of impairment given in the first phase and on an assessment of walking disability and self-care ability.

The EDSS (Kurtzke 1981) is a global rating of neurological impairment consisting of 20 statements that describe decremental reductions in function. The global rating score ranges from 0 to 10, with no impairment (score 0) progressing through signs and symptoms, problems with mobility, upper limb and bulbar functions, and resulting in death due to MS (score of 10).

In practise the lower EDSS grades (0 – 3.5) are defined primarily by variations in grades in the functional systems, while in the upper range of the scale the EDSS

depends primarily on the patient's ability to carry out activities of daily living. In the mid-range the EDSS relies on a not very precise assessment of walking ability (4 – 7): for example, the difference between grades 5 and 5.5 is essentially the ability to walk some 100 metres but not 200 metres. Almost all patients with EDSS scores higher than 5 have walking difficulties and those with score over 6.5 are confined to a wheelchair.

Table 2. 1: Expanded disability status scale

FUNCTIONAL SYSTEMS	SUBSCALE RANGE
Pyramidal	0 – 5
Cerebellar	0 – 5
Brainstem	0 – 5
Sensory	0 – 6
Visual	0 – 6
Bladder and Bowel	0 – 6
Cerebral	0 – 5
Other dysfunctions	0 or 1
Overall EDSS Score	0 – 10

Weaknesses and limitations of the EDSS

In light of the classification already discussed the title is inappropriate because the functional systems concentrate on impairments but include reference to disability and

handicap by including components related to the patient's ability to work and carry out activities of daily living.

As a measure of impairment in MS the EDSS has a number of problems. In several of the functional systems there is lack of precision in the definition of the different grades of impairment. Consider for example, the cerebellar status score: 0 = normal; 1 = abnormal signs without disability; 2 = mild ataxia; 3 = moderate truncal or limb ataxia; 4 = severe ataxia in all limbs; 5 = inability to perform co-ordinated movements due to ataxia. Terms such as "mild", "moderate" and "severe" are not defined or quantified. The scale does not allow for a patient who may have unilateral tremor. It is difficult to use with precision and the reliability of the EDSS scores is therefore questionable.

The process of combining the score in the functional systems with extra data based on the patient's mobility can also be complex, especially in the middle ranges of the EDSS in patients with higher scores in functional systems that do not seriously affect the ability to walk. In the middle and upper ranges there is also a relative lack of sensitivity to potentially important clinical changes that do not affect mobility.

In relation to both its reliability and its responsiveness, the EDSS has been subject to considerable criticism (Noseworthy et al. 1990; Whitaker et al. 1995; Willoughby and Paty 1998). Studies of the reliability of the EDSS have shown considerable inter-examiner variability especially as regards the cerebellar, cerebral and sensory systems. One other area of discontent is the significance of change in the EDSS score. Kurtzke defined patient improvement or deterioration as a change of one point

(Kurtzke 1981; Kurtzke 1983), but Amato *et al* (Amato et al. 1988) and Noseworthy *et al* (Noseworthy et al. 1990) suggest that so small a change may be clinically insignificant or may be due to examiner inconsistency. They argue the need for a 2 point difference (1.0 point on the EDSS and 2 points on the FS).

In the EDSS, the functional systems do not provide a separate assessment of impairment in the upper limbs and are therefore more sensitive to detecting change in the lower limbs. This insensitivity to upper extremity functional status and its change creates a major problem in studies such as this one where the upper limbs were a principal focus of investigation. This weakness of the scale may also enhance the widespread belief that the upper extremities are relatively spared in MS.

The sub-scale for measuring mental state is very crude and was not adequate for use in this study as it was important to ascertain the neuropsychological status of the patients with reliable and valid measures to ensure that the procedure did not result in any deterioration in mental functioning.

Justification for using the Kurtke's FS and the EDSS

> 'The Kurtzke Scale has little to recommend it, and clinical assessment of clinical impairment should be combined with general measurements of disability.' (Wade 1992)

Kurtzke's Functional Systems which concentrate on measuring impairments in MS have been used for many years in studies of patients with MS and continue to be used despite their methodological weaknesses. Although the FS and the EDSS were recently criticized by Willoughby (Willoughby and Paty 1998), MS researchers still

generally regard these scales as the preferred measure of outcome in clinical trials of experimental MS therapies (Noseworthy et al. 1989). However there is widespread feeling that it is time to develop a more reliable replacement particularly for the measure of impairment as defined by the World Health Organisation (WHO) but to date no such scale has been proposed.

Kurtzke's FS and the EDSS were included in this study as they were quick and simple to score once a neurological assessment had been carried out. They are still used by the neurologists in the department as part of the assessment of patients with MS. However separate scales which had been validated on patients with MS were also used to measure impairments which were particularly relevant to this study: namely tremor and cognitive dysfunction.

2.3.2 Quantitative laboratory based measurements

There is a plethora of sophisticated tools with which to measure human motor performance, owing to the proliferation of microcomputers and advances in biotechnology. Involuntary abnormal movements, especially tremor, are particularly amenable to measurement using techniques such as electromyography, accelerometry, computerized maze co-ordination and visually guided manual tracking tests and kinematic studies (Liu et al. 1999).

A large investment of time and money is often required when using sophisticated laboratory-based procedures and all have associated difficulties in measuring complex movement disorders.

EMG can only provide a surrogate marker of limb movement. Signals derived from accelerometry of intention tremor are inaccurate because the finger-nose test provides a non-stationary signal consisting of at most 10 tremor cycles and both the tremor and intended limb movement frequencies overlap. Other disadvantages associated with accelerometry are that accelerometers can only measure activity at one site and record tremor in one spatial dimension (unless complex, expensive triaxial accelerometry is used). In order to assess movement disorders in MS the behaviour of the whole limb in all three planes of movement needs to be appreciated. Despite these problems, accelerometry has become a standard technique for assessing tremor in clinical trials as it provides a quantitative measurement of upper limb tremor. Bain and Findley have shown, however, that accelerometry is not a valid method of assessing the functional significance of postural tremor upon patients (Bain et al. 1993). Tracking tests can be useful for quantifying tremor which involves a single joint but are unsuitable for the assessment of tremors that appear in free limb movements which involve multiple joints (Beppu et al. 1984; Liu et al. 1997) and are therefore of limited use. Kinematic studies can circumvent this difficulty but analysis of the derived signal is complex and limits their widespread use (Findley et al. 1981; Hewer et al. 1972).

In the present study the question being addressed was whether thalamic DBS operation would result in suppression of tremor which would consequently improve the resultant upper limb disability and function. It was decided that simple observation and measurement of the patients' motor behaviour was probably the best form of measurement for this study as it was likely that the majority of patients

referred to the study would be severely disabled and confined to wheelchairs, dependent on carers and hospital transport for attending follow-up assessments. Sophisticated and lengthy laboratory-based measurement was therefore not appropriate or practical.

2.3.3 Subjective tremor-rating scales

A preliminary evaluation of different tremor rating scales, tests of hand function, disability and quality-of-life scales was undertaken at Liberton Hospital in Edinburgh. There were a number of patients under the age of 65 with movement disorders due to MS, who were either in the unit for a short period of respite care or for an in-patient admission for rehabilitation. The researcher carried out a preliminary evaluation of different subjective rating scales and tests of upper limb function so as to examine the strengths and weaknesses of the tests and establish the applicability in a cohort of patients with movement disorders due to MS. This proved to be invaluable in enabling selection of the most practical and appropriate tests and modification if necessary for the purposes of this study. The modifications and omissions made to the published methods are described in detail in this chapter.

The tremor-rating scales that have been used in previous studies and the problems associated with their use for evaluating treatments for MDMS have already been discussed in Chapter 1. Tremor and ataxia are common problems in patients with MS and specific scales have been developed focusing on this patient group (Geny et al. 1996; Speelman and Van Manen 1984) but neither of these scales have been validated. The only tremor-rating scale which appears to have had any formal

assessment of its psychometric properties is Bain and Findley's Tremor-Rating Scale (Bain et al. 1993) and validation was not carried out on patients with MDMS.

2.3.3 (i) Bain and Findley's Tremor-Rating Scale

Bain and Findley's scale (Bain and Findley 1993) scores tremor magnitude separately for different parts of the body and also for different tremor components. It is a combination of a descriptive scale (no tremor, mild, moderate, severe, extremely severe) and a numerical analogue scale (0 – 10). It was chosen after experimentation with several other designs because it proved to be reliable and user-friendly. It is slightly unusual in having more steps than most tremor-rating scales which the authors claim 'tends to improve its precision and reliability'. The scale relies on the examiners having some experience of movement disorders and utilises a cognitive process whereby an observer ascribes a number to a phenomenon to indicate its degree of membership of a set. The scale relates magnitude of the tremor to different anatomical sites (the limbs and head excluding the trunk) and assesses different components of tremor for each of these body parts. The various components of tremor were: rest, postural, kinetic, and intention. The authors avoided the inclusion of measurements of disability and handicap within the scale.

The psychometric properties of the scale were assessed in a study (Bain et al 1993) involving 20 patients with movement disorders due to essential tremor and eight patients with postural limb tremor associated with dystonia. The scores obtained with the scale were compared with the results of upper limb accelerometry, an activity of

daily living self-questionnaire and estimates of tremor induced impairment in writing and drawing specimens.

The inter and intra examiner reliability of the scale was assessed using vidoetape of the patients seen in the assessment clinic and the same four raters. Two video assessments sessions were carried out, the first, one month and the second two months after the initial assessment in the clinic. The rating scale proved to have good inter and intra-examiner reliability for assessing the postural components of head and upper limb tremor and fair to moderate for lower limb tremor. However 'the examiners had great difficulty applying the terms kinetic and intention tremor to real life observations in spite of having previously agreed on these definitions'. For instance the Kappa values for the inter-examiner reliability of right upper limb kinetic and intention tremor components were 0.02 – 0.65 (slight – substantial) and -0.03 – 0.54 (poor – moderate) respectively. Consequently, during the second video assessment 'intention' tremor was not scored, and by confining attention to recording the severity of the kinetic tremor seen midway through a movement, greater inter-examiner agreement was obtained; for example 0.44 – 0.66 (moderate – substantial) for the right upper limb.

The validity of the scale was assessed by measuring the correlation between the mean scores for the different components of tremor in each body part and the results of upper limb accelerometry, activities of daily living self-questionnaire and estimates of tremor induced impairments in writing and drawing specimens which are techniques commonly used in clinical trials evaluating treatment such as drugs on severity of tremor. The results showed that the examiners' scores for the right upper

limb postural component in each patient correlated well with the results obtained from the disability self questionnaire (r = 0.64), and acceleration in the right arm (r = 0.67), as well as handwriting (r = 0.76) and spirography (r = 0.81). In contrast the frequency and acceleration values from right upper limb accelerometry were poorly correlated with disability (r = 0.04), spirography (r = 0.41) and handwriting (r = 0.34). The rating scale therefore produced a reliable method of assessing postural tremor severity, particularly in the upper limbs and head and was a more valid index of tremor induced disability than standard postural accelerometry.

There were limitations of Bain and Findley's Tremor-Rating Scale in relation to using it in the present study. The scale related magnitude of tremor to different body parts but it did not include evaluation of the trunk. Many patients with MS present with truncal ataxia/tremor, the severity of which needs to be assessed. The scale provided a broader gradation system than any other scale but it was found not to be 'user friendly'. It was difficult to make a judgement as not only did the examiner have to decide whether each component of tremor at a given anatomical site was mild, moderate, severe or extremely severe but a numerical score also had to be ascribed to the tremor. The authors also separated kinetic tremor from intention tremor, something which is difficult to do in clinical practice and this was reflected by the fact that the examiners had great difficulty in applying the terms 'intention' and 'kinetic' to real life observations despite having previously agreed on these definitions. The inter-examiner reliability was poor for upper limb kinetic and intention components and this reflected the practical difficulties of defining the boundaries between the kinetic and intention tremor. In addition, the reliability study

had been carried out on patients with essential tremor and 'dystonic tremor', the aetiology of which was nor disclosed but was almost certainly not MS.

2.3.3 (ii) Fahn's Tremor-Rating Scale – methods as published

Fahn *et* al gave a detailed account of his scale in a book called 'Parkinson's Disaease and Movement Disorders in 1988 (Fahn et al. 1988) (see Appendices 2 and 3 for the published FTRS form and definitions of the tremor scale) and, as already discussed, despite the continued international use of this scale there has been no validatory work carried out to assess the reliability, validity or sensitivity of the use of the FTRS in any group of patients. The scale is divided into three parts:

Part A quantifies the tremor at rest, with the patient holding a posture, and with performing action and intention manoeuvres for nine parts of the body (the face, tongue, voice, head, trunk upper limbs and lower limbs). Although the arms are the part of the body most commonly affected by tremor of all types, other parts of the body may also develop tremor. The face, tongue and voice are included as in Parkinson's Disease, tremor usually occurs in the distal muscles but can also involve the lips, chin and tongue. Essential tremor besides appearing in the arms can also appear in the neck and vocal cords. Tremor resulting from a lesion in the superior cerebellar peduncle, referred to as a 'cerebellar outflow lesion' by Fahn *et al*, commonly seen in patients with MS or patients with head injuries, tends to affect the upper limbs, trunk and head.

Severity of tremor in each of the nine body parts is rated in the scale by its amplitude, and is rated as none, slight (amplitude <0.5cm), moderate (amplitude 0.5

– 1cm), marked (amplitude 1 – 2cm) or severe (amplitude >2cm). Whether the tremor is intermittent or always present (a characteristic of rest tremor in Parkinson's disease) is not a factor in the severity score.

Tremor severity is rated for the nine body parts for three situations: rest, maintaining a posture and performing an activity. Rest tremor is assessed with the body parts supported against gravity. This may be achieved in a supported sitting position but in some patients it may be necessary for the patient to lie supine. Tremor of the body part when maintaining a posture is considered a postural tremor. Fahn *et al* assumed a level of sitting ability in patients being assessed with the scale, as the trunk was assessed in sitting (presumably unsupported) or standing. Postural tremor of the arms is observed by having the patient stretch his arms out in front of his body with his elbows extended and then flexed. The authors did not distinguish between these two positions when scoring the postural tremor in the arms but scored them together even though he assessed these two positions separately. Action and intention tremor included goal related tremor and was scored by observing the patient perform the finger nose test and the functional tasks in Parts B and C. No attempt was made to try to distinguish between action, intention and goal related tremors. They were grouped together and scored as one.

Part B of Fahn's Tremor Rating scale includes subjective rating of tasks performed with each hand. These included drawing of Archimedes' spirals (spirography which was incorrectly referred to as 'spirometry' by Fahn *et al*), line drawings and pouring water from one cup to another (volumetric test). Handwriting was also evaluated using only the dominant hand. The quantification of spirography and the line

drawing was based on the crossing of the lines in the figure on the assessment form, 0 = normal; 1 = slightly tremulous; 2 = moderately tremulous or crosses lines frequently; 3 = accomplishes task with great difficulty, many errors; and 4 = unable to complete drawing. There was less space between the lines in the smaller of the two spirals making the task more difficult. Pouring water from one cup to another was also quantified. Cup size and amount of water used in the test were specified to ensure consistency between assessments. The amount of water spilled is the basis for the severity grading: 0 = normal function; 1 = more careful than a person without tremor, but no water is spilled; 2 = spills a small amount of water (up to 10% of total amount); 3 = spills a considerable amount of water (10 – 50%); 4 = unable to pour water without spilling most of the water (>50%).

Part C assesses functional disability. Its items evaluate the severity of tremor with speaking, eating (feeding), bringing liquids to the mouth, hygienic care, dressing and working including homemaking and domestic tasks. These scores, with the exception of speaking, are provided by patients, who are asked to evaluate their ability to carry out these tasks (for definitions see Appendix 2). The speaking score encompasses both voice tremor and 'dystonic adductor dysphonia' as the authors believe that some patients may have both disorders and it is difficult to distinguish between them.

The sub-total scores, i.e. sums of each separate part (A, B and C) are calculated and totalled to give an overall score of all three parts. The maximum possible scores are 80 for Part A, 36 for Part B, and 28 for Part C, making the maximum possible total score 144.

In addition to the quantification of tremor through Parts A, B and C, the scoring form allows for an assessment of overall severity by both the examiner and the patient. This subjective global severity is based on tremor related disability, which is calculated according to the percent of impairment in carrying out all activities of daily living and the cosmetic effect of tremor, which can be psychologically damaging.

2.4 Measurement of MDMS – Methods for Assessing Overall Disability and Specific Upper Limb Disability

2.4.1 Functional Independence Measure and Bathel Index

The Functional Independence Measure (FIM) was devised by a national group of clinical, research and administrative experts in rehabilitation in the United States of America as an instrument for general use in rehabilitation practice (Granger et al. 1986). It was originally developed to measure 18 core areas of function at four levels of dependence, and as such to be a 'minimum data set'. It has since been expanded so that the 18 core areas of function are assessed using a scale that has seven levels of ability. For each item, a score of 1 indicates complete dependence on others to achieve the activity, and a score of 7 represents complete independence (see Appendix 15).

It has been validated in this seven level score format (Hamilton et al. 1994) and it has been shown to have validity in patients with MS (Granger et al. 1990). Granger *et*

al's study (Granger et al. 1990) demonstrated the FIM's sensitivity to differences in patient functional status: the FIM, when compared to a battery of other functional status instruments, was most closely associated with the extent of care required by the MS patients in the study.

The Barthel Index (BI) (Mahoney and Barthel 1965) is the most commonly used tool for recording disability and physical recovery. It is a measure of 10 activities of daily living involving bathing, stairs, dressing, mobility, transfers, feeding, toilet use, grooming, bladder and bowel function. The BI scores are often summed to give a total score which ranges from 0 to 20 in 1-point increments. It has been shown to be a robust, reliable and valid instrument for measuring disability. Its reliability has been studied in several different settings, including a rehabilitation setting (Collin et al. 1998). It has intra-examiner reliability and inter-examiner reliability and is reliable whether the patient is observed performing the tasks or asked about their ability to perform the tasks. The validity of the BI is well established. The score correlates with clinical impression; with motor loss after stroke; and with scores on other ADL indices. Its main use has been with stroke patients.

Justification for using the FIM and the BI

The FIM and the BI were both used in this study. The self care section of the FIM was chosen specifically to assess the patient's ability to perform functional self care tasks with the target upper limb. The FIM was chosen for this purpose as it has seven levels of ranking thus achieving a more sensitive definition of dependence than the BI which has only two or three and is insensitive to small differences (Wade 1992).

One of the main criticisms of the BI is its insensitivity to show change particularly at each end of the scale. It has definite floor and more importantly ceiling effects (Skilbeck et al. 1983; Wade 1992) however the majority of patients with MDMS were moderately to severely disabled so the fact that there were few challenging tasks at the higher end of the scale was not anticipated to be a problem.

The FIM also scores some activities of daily living (eating, drinking, grooming, dressing, toileting) individually. The FIM therefore permitted a more precise description of the levels of dependency produced by the patient's movement disorder and according to Granger it is the most useful tool in predicting the burden of care in MS (Granger et al. 1990). FIM training videos were available and were used to teach the researcher to use the scale to evaluate self-care activities for daily living.

The FIM scale also covered areas of communication, social integration and cognition which the BI did not, but the researcher did not score these areas. There were time constraints imposed upon the researcher at the initial assessment owing to the time required to carry out the extensive battery of tests assessing severity of tremor and function of the target upper limb. A trained neuropsychologist carried out an assessment to establish the cognitive dysfunction at the initial assessment using a valid and reliable neuropsychological test battery.

The absence of scoring for fatigability, vision and sexual function are notable omissions in both the FIM and the BI and both scales therefore lack specificity for MS. It was therefore necessary to include a separate scale for fatigue as disorders of movement can influence levels of fatigue in MS.

The major focus of this study was to find out whether tremor causing functional disability of the upper limb, head and trunk could be reduced by thalamic DBS. Specific tremor-rating scales and tests of upper limb performance (JTHF) and function (Self-care section of FIM) went part of the way to serving this purpose. However, it was also important to include an overall measure of patient disability because there can be major interactions between tremor and the neurological deficits found in multiple sclerosis. It was essential to classify the group of patients in the study by identifying their general level of functional disability before and twelve months after the implant of the thalamic DBS. It was anticipated that the surgical procedure might eliminate tremor but it was also important to establish that in doing so it did not also adversely affect aspects of other function.

The BI was used for this purpose as the scoring was simple and only took a few minutes. The FIM took 20 minutes to complete and was also designed to be completed by a multi-disciplinary team and therefore would have been used out of context in this study. Both the FIM and the BI are ordinal scales with a rudimentary scoring system which should not be summed to give an index score although this is commonly performed in studies. Valuable information is lost by summing the different items.

Quantitative tests of neurological function (QENF) pioneered over a period of two decades by Tourellotte and Syndulko (Touttellotte and syndulko 1989; Syndulko et al. 1993) were also considered. The basis for these tests is the timing of a series of measurements of co-ordination that challenge the neural systems most often affected

in MS. However they have not made major inroads into the routine evaluation of MS.

The advantages of these tests were reported to be that motor function in the arms and legs could be scored separately and that the tests were reliable on repeated testing if carried out by a trained member of staff. The tests have been extensively evaluated in a two year follow up study involving 55 patients with MS. Unfortunately, although some of the more simple behavioural challenges seemed appropriate for our patients, eg. the simulated activities of daily living, the majority of the components were totally unsuitable: finger tapping and foot tapping are often used as tests for dysdiadochokinesia but they are of questionable clinical significance; the Perdue peg board proved too taxing for our patient group; standing in balance on two legs with eyes open then closed, standing in balance on one leg with eyes open then closed and tandem gait were primarily concerned with co-ordination associated with equilibrium and were presumably developed for quantifying sensory ataxia rather than motor ataxia.

2.4.2 Sitting, Standing and Walking Tests

2.4.2 (i) One minute sitting balance

A test to determine the extent of trunk control when in a vertical position did not exist. Full control of independent sitting balance requires patients to be able to maintain an upright posture using normal postural adjustment mechanisms during or after being displaced by an external force. A subject may maintain a sitting posture that is biomechanically stable by collapsing into flexion at the thoracic and /or

lumbar spine. Alternatively, an upright posture may be obtained by cross-bracing with hands on thighs. This is a sitting posture which is commonly adopted by MS patients with truncal ataxia, in an attempt to gain some truncal stability when they are forced to sit unsupported. It is important to realize that this posture can be maintained in the absence of joint control at the trunk and hips but that it is not a functional position as patients are unable to free their arms. It was therefore important to adopt a standardized definition of independent 'normal' sitting balance for the purpose of this study.

Previous studies of sitting balance reported in the literature have weak definitions of 'sitting'. A classic example is provided by Beals (Beals 1966) in a study evaluating prognostic indicators for walking in children aged 9 months with cerebral palsy. Beals defined sitting as 'sits alone for 5 – 10 minutes'. This gives no indication of trunk posture or hand support and thus no valid indication of control status. A biomechanically valid test of independent sitting balance was defined in a study by Butler (Butler 1998) as: 'sitting on a bed with head erect, eyes looking forwards, trunk erect and not slumped with minimal flattening of the lumbar spine, thighs to remain in contact with the bed and no hand or arm support on bed, thigh or body and independent sitting balance maintained for 60 seconds. ' It was used for the purposes of this study and was scored as a pass or fail.

2.4.2 (ii) 10 second standing balance

The patient was observed attempting unsupported standing in balance for more than 10 seconds. Physical help was permissible in making the transition from sitting to standing, but not during the timing period.

2.4.2 (iii) Ten metre walk

The patient was observed walking a measured distance of 10 metres. The patient commenced the walk from a standing start, from a predetermined spot and was instructed to walk to a point at the end of the walkway. Timing was started at the beginning of the first step and finished as the patient crossed the mark indicating the end of the walkway. The examiner walked next to the patient on the tremorous or more tremorous side. If appropriate, a walking aid was used but verbal cueing was avoided. Verbal instruction was standardized to '*I would like you to walk to the far end of this room at a speed that is comfortable for you, and I will time how long it takes*'.

Justification for these methods

Many of the patients referred for thalamic DBS had truncal ataxia and truncal instability. This initially proved to be problematic to measure objectively as there were no specific tests for truncal ataxia. However the concept of using appropriate tests of neurological performance where the behaviour in response to specific challenges was objectively evaluated, presented a useful way of assessing the control of the trunk in these patients. The patients' performance of three simple tests of sitting, standing and walking were compared to an initial 'baseline' score for each

activity, to determine any change over time. The protocols adopted for these tests (Appendix 16) were based on the standardized measures of simple functional movement used to measure the mobility outcome after stroke (Smith and Baer 1999).

These tests had face validity and the 10 metre walk has been shown to be reliable (Wade 1992). It was anticipated that if there was a dramatic change in the severity of truncal ataxia as a result of the surgical procedure this might impact on the patients' ability to perform the tests successfully. Each test was scored simply as a pass or fail and the time taken for the patient to perform the test was recorded.

2.4.3 Objective Tests of Upper Limb Function

2.4.3 (i) Tests to measure focal upper limb function

> 'The measurement of arm function initially seems difficult because the arm and hand have so many uses from gesture through balance, gross strength related function and on to fine manual dexterity' (Wade 1992).

The ability of a patient to use his hands and arms effectively in everyday activities is dependent upon not only co-ordination but anatomical integrity, mobility, muscle strength and sensation. It is also influenced by age, sex, mental state and by disease processes not only affecting the hands and upper limbs but other areas also.

One approach to testing arm disability is to measure (in detail) the patient's performance of one single skill. Normative values are available for these tests which are useful in the diagnostic process if the patient is suspected of a movement disorder affecting the upper limbs. These tests also give a better impression of the course of a disease affecting movement rather than relying solely on clinical judgement and are therefore helpful in following patients' progress in clinical trials.

Four tests are discussed: Nail and peg/box and block tests; tapping tests and the spiral test.

Nail and peg and the box and block tests

These are timed tests where the patient is required to pick up either nails (Verkerk et al. 1990) or wooden dowels (Goodkin et al. 1988) and place them accurately into holes on a wooden board. The box and block test (Mathiowetz et al. 1985) involves picking up blocks of wood and transferring them from one part of a box to another and has been used in studying deterioration in MS (Goodkin et al. 1988) . In the nail test, described as a test to assess co-ordination, the subject has to move 32 nails from one side of a board with 64 holes, to the other. The total score is the number of nails moved in 30 seconds. The authors reported that the test was highly reproducible in healthy subjects. However owing to small patient numbers the reliability in patients was questionable.

The nine hole peg test is a standardized, reliable, valid and rapidly administered test of upper extremity function which is used frequently for Parkinson's disease or ataxia (of any cause) (Wade 1992), particularly in out-patient clinics. Age-related data are available for neurologically normal subjects (Mathiowetz et al. 1985). The test has been used in clinical studies (Goodkin et al. 1988) and has along with the box and block test been shown to be more sensitive in detecting changes in upper extremity function in patients with MS than the EDSS. The test scores the ability to manipulate pegs. The patient is required to pick up nine wooden dowels and place them into a wooden base with nine holes in any order until all the holes are filled.

They then have to remove the pegs one at a time and return them to the container. An observer times from start to end. The test is a measure of finger dexterity but can also be used to measure the disabling effects of sensory loss and ataxia, two impairments which according to Wade (Wade 1992) are difficult to measure in isolation.

Tapping tests

Various tapping tests have been developed in an attempt to quantify cerebellar dysfunction. They are based on a decreased capability to make quick alternating movements (dysdiadochokinesia). In the so-called finger tapping test the patient is instructed to tap successively the key of a computer with the index finger for 15 seconds (Schimoyama et al. 1990). The study yielded information as to what extent age, handedness and sex may affect motor function in normal subjects. Tapping frequency distinguished the normal control group from abnormal groups (ie. patients with pathology) but it could not distinguish one abnormal group from another. Notermans *et al* (Notermans et al. 1994) described a tapping test for the upper limbs where a device is used consisting of two push buttons placed at a fixed distance apart and connected to a computer. The patient is asked to push the left and right buttons alternately with the index finger as fast as possible for 15 seconds. The test is simple but it seems to be unreliable (Heller et al. 1987) probably because it is greatly affected by motivation and therefore is not recommended (Wade 1992). The reliability and validity of these tests has not been reported in detail.

Spiral tests

The spiral test is described along with the nail test by Verkerk *et al* (Verkerk et al. 1990). These tests are used in the Department of Neurology of the Academic Hospital in Groningen to measure co-ordination of the hands. A sheet of paper (size A4) is used on which two spirals are printed; the distance between the lines is 1cm (Appendix 7). The subjects must draw as quickly as possible a line from the starting position (the arrow) to the central point, without touching the spirals. The total score is the time in seconds needed to perform the test, with 3 seconds added for each time a line is touched and with 5 seconds added for each time a line is crossed.

Limitations of the focal tests of upper limb function

Although these tests are frequently used to assess tremor related disability in the upper limbs of patients with movement disorders it was apparent after experimenting with using the tests with patients with MDMS that they were not suitable for this patient cohort for the following reasons. A major problem with MS patients with advanced disability is associated disuse atrophy. Many of the patients were unable to manipulate small objects such as a pen or wooden dowels because of poor finger function which could result from a variety of factors such as impaired proprioception in the hand, altered muscle tone and muscle weakness. Also, in many cases the movement disorder was so severe that the violent uncontrolled moments of the upper limb did not allow the patient to pick up or place one peg or to rest a pen on a piece of paper on a table let alone attempt to draw a spiral with it. If drawing a spiral was possible, the spirals encorporated in Fahn's TRS were preferred as they were easier

to complete than the one described by Verkerk *et al* (Verkerk et al. 1990): they required the patient to complete only three circles of a spiral as opposed to six which tended to cause fatigue. These tests may also be affected by other factors such as lack of motivation, visual disturbance or sensory problems which are common in MS (Bauer 1978).

It was often frustrating, demoralizing and tiring for patients to be asked to perform many of these tests because the tests required the patients to possess a background level of postural control in the upper limb which many of the patients did not have. Also some researchers question the clinical relevance of some of these measures of focal upper limb function. Therefore these tests were considered to be inappropriate.

2.4.3 (ii) Test Batteries to measure upper limb function

There are many different methods of measuring arm and hand function and, from studies performed, there does not appear to be one preferred method (Blair 1999). There are many tests which contain a greater or lesser number of individual items that measure the general ability of a patient to perform upper limb tasks which depend upon well-preserved use of the arm. These tests use common activities to simulate movements which may be used in ADL. None has been specifically developed for use with patients with multiple sclerosis.

Tests which assess the hand by means of functional tasks are concerned only with the subject's ability and speed of performance, whilst the 'quality' of movement and performance are not rated. This is an advantage when using such tests to document

clinical change in response to treatment as difficulties in measuring the 'quality' of movement, based on an unclear norm, do not arise.

Jebsen Test of Hand Function

Jebsen (Jebsen et al. 1969) devised a series of seven standardized and objectively measured subtests to provide an objective measurement of hand function which was based on performance in a normal population. It was designed for both clinical and research use. The tasks making up the test were chosen as those representing hand function commonly used in ADL. The time of performance is recorded for each sub-test. Tasks used may be grouped into those requiring fine manipulation and those requiring gross handling. The subtests requiring the use of fine manipulation include: writing, turning cards over, picking up small objects and placing them in a can, a simulated feeding task and stacking draughts. Those using gross movements are placing large empty tins and large weighted tins onto a set target. The test takes approximately 20 minutes.

In the original article, Jebsen *et al* reported British norms which were developed on a sample of 360 normal subjects. Mean times and standard deviations for normal subjects were presented in two large groups (ages 20-59 and 60-94) for each test item. The JTHF has also been standardized on an American population (Agnew and Maas 1982a; Agnew and Maas 1982b) for use with patients with rheumatoid disease.

To evaluate the reliability of test results in a given individual, 26 patients with stable hand disabilities were tested on two occasions. The sample population consisted

largely of neurological patients although none of them were patients with MS. The results of the reliability study reported in the original paper by Jebsen showed that fair to excellent reliability was found for each subtest. Validity of the JTHF was not evaluated by the authors.

A recent study by Jones (Jones 1986) of 548 patients with neurological conditions, 56 of whom had intention tremor, showed that the consistency and repeatability of the JTHF was very high in keeping with Jebsen's findings. However an evaluation of content validity was carried out through an analysis of hand movements and grips used by normals and patients on the JTHF and ADL (dressing and feeding) and it was found that there were no typical hand movements used in either the JTHF or ADL testing of the patients. In analysis of hand grips used by patients and normals on the JTHF and ADL, again a wide variation was found. Common grips could be identified but once again no 'norm' was found.

Jones (Jones 1986) showed that the JTHF was not a valid test of grips used in ADL, as originally described by Jebsen and argued that the usefulness of the test in a clinical setting must therefore be other than a measure of grips used in ADL.

The test therefore does not use hand movements/grips used in ADL, other than by chance. Nor does the JTHF correlate with ADL function. Jones cautions that the test cannot be seen as a predictor of ADL performance but that the power of the test is in its ability to detect neurological deficit and show change in the severity of the deficit.

The JTHF has been used in many studies in the past years. It has been used after stroke (Jebsen et al. 1971; Spaulding et al. 1988), to monitor the effect of wrist

motion on time required to complete manual tasks in normals and patients with peripheral nerve injury (Carlson and Trombly 1983), to evaluate the correlation between the functional ability and the number of joints affected in osteroarthritis patients (Labi et al. 1982), and to evaluate the effect of therapy in patients with chronic MS (Jones et al. 1996).

Chyatte (Chyatte and Birdsong 1972) used the JTHF as a comparative measure in a study to evaluate a time and motion measurement system. This system was designed for use in the assessment of motor performance of the upper extremity. A high correlation was found between their predicted times and the actual standard time of performance on the JTHF. Using their movement analysis it was found that each of the subtests of the JTHF used different hand skills (e.g. those groups of hand movements used for card turning were different from those used for simulated feeding).

The JTHF has also been used in a longitudinal study of the recovery of head injured patients (Panikoff 1983). Results of this study indicated that the JTHF showed changes in patients' status up to six months after injury.

2.4.4 Measurement of MDMD – Methods for Assessing Handicap

2.4.4 (i) The London Handicap Scale

The London Handicap Scale (LHS) (Harwood et al. 1994a) uses the system description given in the ICIDH. This has 6 'dimensions' (mobility, orientation, occupation, social integration, physical independence and economic self-sufficiency) on which the instrument generates a profile of handicaps, and an overall handicap severity score. The definitions for each dimension are generally self-explanatory, but need some clarification. *Mobility* is the ability to get from one place to another, using whatever help, aids or means of transport that are normally available. The disadvantage associated with being reliant for help on aids or another person for help is covered under *physical independence* handicap. *Orientation* is the ability to perceive and understand one's immediate environment, including thinking, perception and communication. *Occupation* is doing what one wants or needs to do with one's time, including work, housework and leisure activities. *Social integration* describes the ability to maintain relationships with other people in the face of ill health. *Economic self-sufficiency* includes both the effects of ill health on the ability to earn a living and the use of resources to overcome disadvantages associated with ill health.

A questionnaire has been written based on these dimensions, each of which has six levels arranged in order of increasing disadvantage (Appendix 17).

The questionnaire emphasises what a patient is able to achieve in everyday life in his normal physical environment, regardless of the help that might be required (eg. human assistance, aids or adaptations). The scoring system was developed using a novel marketing research approach called 'conjoint analysis' and has weightings based on the opinions of a large representative population of healthy people. Once the classification questionnaire is completed, six numbers (each representing a level on a dimension) describe each individual. The appropriate score for each level of each dimension is then applied and entered into the formula:

Handicap score $= 50.5+u_m+u_{oc}+u_{pi}+u_{si}+u_{or}+u_{ess}$

where $u_m, u_{oc}, u_{pi}, u_{si}, u_{or}, u_{ess}$ are the scores of the appropriate level of each dimension given in the scale weighs table (Appendix 18) and 50.5 is a constant. This results in a score between 0 and 100, with 100 representing no disadvantage and 0 the maximum possible disadvantage.

2.4.4 (ii) Handicap Questionnaire

The Handicap Questionnaire (Appendix 19) provides a quick and useful qualitative insight into the social consequences of having tremor. It was devised by Bain and Findley (Bain and Findley 1993) and used in a study evaluating tremor in patients with essential tremor (Bain et al. 1994).

The patients were asked to answer the questions by putting a circle around the appropriate letter and scored 1 for answering yes and 0 for answering no. This resulted in a total score out of 9. The higher the score the greater the level of handicap.

Justification for these methods

The development of a useful handicap scale has met with mixed success. The number of handicap scales appearing in the past few years has increased significantly. Some of these are listed and discussed in the article by Harwood et al (Harwood et al. 1994b). A handicap scale was included in the Minimal Record for Multiple Sclerosis (Kurtzke 1981; Thompson et al. 1990). It was called the Environmental Status Scale (ESS) and was intended to assess handicap more specifically by grading a person with MS in terms of their work, financial situation, home transportation, community assistance and social activity. However the Environmental Status Scale has not gained wide acceptance in MS research.

Although many patient based QOL questionnaires had been developed over the last decade, only one, the Disability Impact Profile (DIP) specifically addressed MS. The DIP (Lankhorst et al. 1996) is a self administered questionnaire concerning 39 abilities/activities with parallel questions about (dis)abilities and their importance or impact on the patient. Its use provides a profile of weighted scores measuring quality of life (with a maximum QOL of 1.0 and a minimum QOL of 0.1). In this way disability assessment is supplemented with information about subjective perception.

The reliability, validity and sensitivity of the DIP has recently been assessed. A study involving 43 patients with MS in Denmark (Jonsson et al. 1996) evaluated the DIP as a measure of QOL and as a measure of outcome. The authors concluded that the DIP seemed to be a promising instrument which may help to focus efforts on the rehabilitation of patients with disabilities with a high impact on QOL. However, they

also reported that some patients complained that the DIP was difficult and time consuming to complete. It was therefore decided that it would not be suitable for use in this study.

The Functional Assessment of Multiple Sclerosis Quality of Life Instrument (FAMS) (Cella et al. 1996) and The Multiple Sclerosis Quality of Life Instrument (MSQOL-54) (Vickrey et al. 1995) have recently been developed as MS-specific QOL instruments. The FAMS was developed as an extension to the Functional Assessment of Cancer Therapy Instrument so that many of the items are not disease specific, though those that are were generated via patients, providers and a literature review. The MSQOL-54 comprises the short form 36-item health survey questionnaire and 18 additional items that are condition specific. The authors provide evidence of the reliability and validity of both measures though no evidence of responsiveness is given. Results of studies reporting the use of these scales were only evident at the time or shortly after this study commenced and therefore they had not been widely used. Also both are lengthy questionnaires involving 44 and 54 items respectively and they would therefore not have been suitable.

More research is needed to develop clinically useful, valid measures of handicap specific to patients with MS as none exists at present. The London Handicap Scale which, although not specific for MS, seemed to have many of the criteria required to be a useful measuring tool for handicap associated with MS and was therefore chosen for use in his study. It has been carefully formulated to be quick and easy to complete by the patient or carer or both. It requires a choice of one of six levels for six parameters of handicap. It has been used in many studies and has undergone

rigorous evaluation of its psychometric properties. The Handicap Questionnaire was also used as it was quick and easy to complete and gave some insight into the social consequences of living with a severe disorder of movement.

2.5 Measurement of MDMS – Methods for Assessing Aspects of QOL Relevant to this Study

2.5.1 (i) Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (Zigmund and Snaith 1983) (HAD) was designed for use in non-psychiatric hospital departments to screen for anxiety and depression. The questionnaire includes fourteen items which most accurately reflect the person's own feelings in the week prior to assessment. Each response is allocated a score from 0 to 3 using a score sheet (Appendix 20) and separate totals are obtained for anxiety and depression. The HAD indicates the probability of a patient having a mood disorder: a score of between 0 and 7 indicates that there is *probably* no evidence of mood disorder; between 8 and 10 is a borderline area suggesting that mood disturbances *might* be present; a score of higher than 11 indicates the *probable presence* of mood disorder. The highest possible score for anxiety or depression is 21.

Justification for use of the HAD

MS is the leading cause of disability in young and middle aged adults and is not surprisingly known to be associated with a high risk of depression. Depressive symptoms of sufficient severity and duration to warrant a diagnosis of major

depression affect up to half of patients during the course of their illness (Sadovnik et al. 1996). The prevalence of depression in MS exceeds that reported for other neurological disorders (Schiffer and Babigian 1984). Depression in multiple sclerosis has a complex multifactorial pathogenesis. Evidence has emerged that increased social stresses and inadequate family and community supports are important (Feinstein et al. 1992). It is currently unclear how much of what is called mental or emotional change in MS is due to organic changes in the brain and how much is due to the patient's response to the disease (Matson and Brooks 1977). The past decade has undoubtedly brought a greater awareness of the behavioural sequelae of multiple sclerosis. However, owing to the problems already highlighted with the continuing use of the EDSS to assess patients with MS and the fact that it affords little weight to psychopathology, the risk remains that depression is often not properly assessed.

It was important to try to gain some insight into the emotions of patients undergoing thalamic DBS for DMMS as it seemed reasonable to expect a decrease in anxiety and depression in patients if the outcome of the operation was favourable.

There was an assortment of measures that could have been used to screen for a mood disorder including a variety of observer and self-rating scales. Observer checklists were considered to be inappropriate, as they usually require familiarity with the patient's behaviour over a wide range of everyday activities. Patient contact was relatively limited in this capacity as the emphasis at assessments was on measuring of severity of tremor and upper limb function. A self rating scale such as the HAD was ideal for the purposes of this study because the patients were sent the questionnaires which they completed at home and then brought with them to the

hospital on the day of their formal assessments. The evaluation of mood took place before the operation and then again 12 months after it.

2.5.1 (ii) Neuropsychological Assessment

A brief validated neuropsychological screening and monitoring test in routine use in the Department of Clinical Neurosciences (Taylor 1997) was slightly modified to be suitable for use in patients with severe tremor. The original collection incorporates the Mini-Mental State Examination (Folstein et al. 1975) , almost all of the tests recommended by the Medical Research Council Workshop Steering Committee (Medical Research Council Alzheimer's Disease Workshop Steering Committee 1989) concerning Alzheimer's Disease (two questions from the latter concerning people famous in the past having been replaced), and various other tests found useful in neuropsychological practice (Taylor 1997). The original form of the test collection required the person to:

- answer orientation questions concerning time, place, person, and current affairs
- repeat three words
- subtract 7s serially from 100
- recall the three words given
- repeat a name and address
- recall contents of last meal, a recent news item, name of last school attended, name of any teacher there
- spell 'world' forwards and backwards
- recall the given name and address
- copy a figure (overlapping pentagons)

- write a sentence
- recall (i.e. draw from memory) the figure
- complete a paper-and-pencil maze, and then a similar choice-free maze if necessary
- draw a clock face
- attempt the Weigl sorting test (Weigl 1941)
- name or identify colours and shapes
- carry out five spoken verbal commands of variable length and complexity
- carry out then read aloud two written verbal commands printed on cards
- repeat the phrase 'No ifs ands or buts'
- pretend to wave goodbye, and brush teeth
- name or identify five body parts and five objects
- identify three objects photographed from unusual angles
- produce names of animals for one minute
- produce words beginning with the letter F for one minute
- say how three pairs of items are similar (from (Wechsler 1981))
- attempt four cognitive estimation items (from (Shallice and Evans 1978))
- recall the three words given earlier, the given name and address and the given figure.

This original collection, with appropriate weighting of scores such that different aspects of mental functioning are substantially represented in the total score, yielded a total score out of 210. It has been shown to be sensitive to the presence of brain dysfunction of various types and in various locations (including subcortical), to be reliable, to be sensitive to change over time, and to significantly relate performance

on other neuropsychological tests and to ratings of everyday mental functioning made by neurological and neurosurgical patients themselves and ratings made by their relatives or carers.

In the present study, minor modifications to normal materials or procedures were made in the mazes and Weigl tests to allow for tremor. Drawing a clock face and writing were often omitted because of severity of tremor. Copying a design and drawing it from memory were replaced by simple multiple-choice perceptual and recollective versions of these tasks. For purposes of analysis, scores in the omitted tests were omitted for all patients (even for individuals who could make a valid attempt at one or more of those tests), and each patient was consequently assigned a score out of 174. The majority of patients (i.e. those with adequate visual acuity) also completed a short yes-no face recognition test (in routine use in this department) comprising presentation of ten target faces amongst ten filler items followed by recognition testing of the ten targets presented amongst another ten fillers. The pattern of results in this group of patients was essentially the same whether or not the score from the face recognition test was included (by adding it to the total as described above), so data from this test will not be considered further here.

Most patients who had stimulator implantation completed the test collection at varying intervals before surgery and approximately four weeks after it. Most patients who did not proceed to stimulator implantation completed the test collection once only, during the initial study assessment period. All testing was carried out by one experienced clinical neuropsychologist.

Justification of the methods used

It is now recognized that cognitive dysfunction is a common symptom in MS occurring in between 43 and 65 percent of patients (Beatty 1993; Rao 1986). The cognitive impairment may be subtle and simple bedside tests of higher mental function commonly used to screen for dementia are not sufficiently sensitive for the purpose although they contain more detail than the assessment of mental state included in the EDSS.

Various very brief indices of cognitive impairment have been developed, primarily for use by non-psychologists, most of which only take a few minutes to administer. Traditional screening tests like the Mini-Mental State examination (MMS) (Folstein et al 1975) which are useful in assessing 'cortical' dementia like Alzheimer's disease, have proved to be relatively insensitive to the cognitive deficits of MS (Beatty and Goodkin 1990). This is not surprising since MS does not produce gross language disturbance or a dense amnesia as would be observed in a cortical dementia. Instead MS results in a failure of retrieval (rather than a problem with storage) and impaired performance on measures of abstract reasoning, sustained attention, speed of information processing, visuospatial skills and verbal fluency (Peyser et al. 1990).

Cognitive deficits have not been identified in any of the studies of thalamic DBS reported in the literature to date. However, in the review by Haddow et al (Haddow et al. 1997) transient confusion or other psychic symptoms were recorded in 6.7% of patients with MS undergoing stereotactic thalamotomy for tremor. The psychic

symptoms were not permanent in any of these cases. There was therefore a need in this study for a moderately brief cognitive screening test that could not only discriminate cognitively impaired from cognitively intact patients but also detect any changes in mental functioning in the patients undergoing stereotactic surgery. It was essential that the test did not require the large investment of time inherent in a detailed neuropsychological assessment, but that it should provide broader or better information than was given by brief screening tests currently available. The brief neuropsychological assessment was found to be practical, informative and sensitive to change in the cases of patients undergoing stereotactic surgery.

2.5.1 (iii) Fatigue Severity Scale

The Fatigue Severity Scale (FSS) (Krupp et al. 1989) was originally designed to measure fatigue experienced by people with MS. It is a list of nine statements designed to assess perceived fatigue (Appendix 21). Each statement (eg. 'I am easily tired') is rated on a scale of 1 (strong disagreement) to 7 (strong agreement). The individual's score is the mean of the numerical responses to the nine statements. Krupp and colleagues found that healthy adults scored 3.3 ± 0.7.

The FSS has been found to identify successfully features of fatigue specific to the medically ill and to distinguish between normal cohorts and patients with fatigue related to MS. The FSS has been shown to have internal consistency, reliability, stability over time, and sensitivity to clinically significant change (Krupp et al. 1989). .

Justification for use of the FSS

Fatigue is a common complaint reported by many people with multiple sclerosis. In fact, studies by Kraft (Kraft et al. 1986) and Layward (Layward et al. 1989) have shown fatigue to be the most common symptom. Fatigue is not only frequent but also appears in most patients. It has been estimated that 78% to 89% of patients with MS experience symptoms of fatigue (Krupp et al. 1988) yet it is surprising that Kurtzke does not include this symptom in the eight functional systems of his scale (Kurtzke 1983). Fatigue is not necessarily a permanent symptom of MS. It may vary not only daily but hourly as well. In clinical practice it is customary to find patients with significant fatigue, which may be severe enough to cause disability (Monks 1989) .

Several trials have been performed to evaluate fatigue in multiple sclerosis. Different authors have used visual scales (Weinshenker 1992) and subjective scales (Van Diemen 1999) (Desrouleux and Weinreb 1999) to evaluate fatigue in therapeutic trials but the most extensively used scale, has been the Fatigue Severity Scale (FSS), which was proposed in 1989 by Krupp (Krupp et al. 1989) . Recently however, a new scale, the Fatigue Descripive Scale (FDS) (Iriarte and de Castro 1994) has been proposed which has been designed specifically to measure the severity, and to define some characteristics of MS fatigue. It enables the clinician to find out if the fatigue is important enough for the patient to manifest it openly, how it shows up, how often it happens and what limitations the fatigue produces. The FDS may thus have proved useful for the purpose of evaluating the different characteristics of fatigue. Measuring fatigue as a single number as with the FSS provides some information but is not really enough to indicate how the fatigue really affects the patient; nor does the

number itself give a clear idea about how severe or frequent the fatigue is. The FDS appears to address these factors but unfortunately it was first published in 1994 and therefore was still undergoing preliminary evaluation at the start of this study. It has since been validated and used in several published studies by its authors (deCastro et al. 1995; Iriarte et al. 1996).

Reducing fatigue may be an objective of treatment of thalamic DBS in MS patients with severe disorders of movement. In patients with large amplitude and more complex tremor, it appears reasonable to adopt a limited objective which can consist of reducing the state of fatigue induced by tremor and restoring minimum use of the upper limb (Nguyen et al. 1996).

Geny (Geny et al. 1996) found in his study that almost all patients claimed that the fatigue they experienced while performing some activities of daily living decreased in relation to relief of tremor although fatigue was not measured specifically. It was therefore important to measure the severity of fatigue in this present study and the FSS was used for this purpose.

2.5.1 (iv) Assessment of patients' opinions of the operation

The patients were asked to give their opinion of how they felt about the operation at the 12 month post-operative evaluation (Appendix 22). They were given the choices of feeling enthusiastic, satisfied, moderately positive or negative about the outcome of the operation and asked to circle one of the words.

Justification for the methods

It was vital to include the patients'assessment of the result of the operations as not only has research shown that professionals are relatively poor judges of both the degree of disability experienced by patients and the impact that this has on their lives but Bond and Thomas (Bond and Thomas 1991) have also shown that an outcome perceived as positive by staff, may not be perceived as such by a patient. A self-assessment form was therefore used which had been previously in a study evaluating stereotactic thalamtomy for the relief of intention tremor in MS (Speelman and Van Manen 1984). This was completed by the patients at the twelve month assessment.

2.6 Summary

Validated scales existed for measuring disability, handicap and QOL in patients with MS. The influence of MDMS on these dimensions was important to address as there was a dearth of information in these areas.

There was no validated scale available however for measuring MDMS. The lack of such a scale presented a major problem for this study as, in order to clinically evaluate the effect of thalamic DBS, a scale was required for measuring MDMS that had known validity, reliability and responsiveness. Therefore one of the most important aims at the beginning of the study was to develop and validate a scale for measuring MDMS for the purposes of assessing and objectively measuring movement disorders in patients with MS who were referred for (potential) therapy

using thalamic DBS. The next two chapters of this thesis respectively discuss the development and validation of the tremor-rating scale that was chosen for use in the present study.

CHAPTER 3

DEVELOPMENT OF TESTS TO MEASURE MOVEMENT DISORDERS IN MS

3.1 Development of a Tremor-Rating Scale for the Study

Fahn's Tremor-Rating Scale was chosen for use in the present study. The strengths, weaknesses and justification for using the scale will be discussed. The methods used were a modification of the existing methods originally described by Fahn (Fahn et al. 1988) and details are given of the modifications that were made.

3.1.1 Strengths, weaknesses and justification for the use of FTRS

Fahn's Tremor Rating Scale was designed for use predominately with patients with Parkinson's disease rather than with MS patients specifically. Consequently there were several limiting factors that needed to be addressed before it could be used with a cohort of MS patients.

Tremor is the only presenting symptom in patients with essential tremor. FTRS is appropriate for use with these patients since there is no need to follow the progression of other symptoms of the disease. This is not the case in Parkinson's disease or MS where the patients present with other neurological symptoms. FTRS has been used in studies with Parkinson's patients but its use was supplemented by

use of the Unified Parkinson's Disease Rating Scale (Lang and Fahn 1989) to follow symptoms other than tremor, relating to the disease. MS is a diffuse disease often affecting many areas of the CNS and therefore causing other symptoms to arise apart from tremor. Therefore, in order to assess the full extent of the disease a complete neurological assessment was also required.

Patients with MS frequently present with a cerebellar syndrome, which usually affects the proximal, more than the distal muscles. The head and trunk may also be involved. It is therefore important to distinguish between the severity of tremor in the proximal and distal muscle groups. Although in the original article, Fahn assessed these postural muscle groups separately, he scored them together. He did not attempt to separate goal-related movements from action/intention movements. It would appear that it is important to do this as the kinetic tremor seen in patients with MS persists or worsens with goal directed movement (Hallet 1986) .

The controversy over this issue has already been raised in Chapter 1, and for the purposes of this study it was decided that action (which was termed 'kinetic' in this study, in keeping with the TRIG classification (Findley and Koller 1995)) and intention tremor should be assessed and scored as one. However goal related tremor is tremor that occurs to any significant extent during the performance of a task and in MS patients should be considered separately from action/intention tremor.

Standard sets of conditions and definitions for tremor and its severity are provided to help to ensure consistency not only between assessments by the same examiner on different occasions but also among different examiners. The emphasis tends to be on

assessing the upper limbs presumably because patients with Parkinson's disease and essential tremor do not generally present with movement disorders affecting the trunk. There are therefore only minimal instructions for assessing the head and trunk. Patients with MS often have severe problems owing to titubation of the head and truncal ataxia which results in truncal instability and the inability to sit unsupported. It was therefore felt that these guidelines were not explicit enough for use in this study.

Basing the severity of scoring the tremor on the size of its amplitude as specified by Fahn had its limitations as the amplitude ranged from zero to only two centimetres. The tremor commonly seen in MS patients tends to have large amplitude flailing movements and the magnitude of tremor amplitude offered by the scale was going to be inadequate to measure the tremor in MS patients.

Certain parts of the scale such as the inclusion of the assessment of tremor of the face or tongue were not appropriate as movement disorders affecting these areas of the body are generally not problematic in patients with MS.

There was a large emphasis on writing tasks in the original scale that included handwriting, line drawing tests and drawing of spirals. Holding and using a pen may be difficult for many patients with MS as a result not only of tremor but also owing to other limiting factors such as sensory impairment, muscle weakness and abnormal muscle tone. Fatigue was also a major physical handicap in many of these patients with severe movement disorders. It was therefore apparent after trying out these tasks included in Fahn's TRS with some patients with MS that it was going to be

impossible to incorporate all of these tasks because of the severity of disability of the patient group. Fahn *et al* standardized the test procedure to make the tests more sensitive by stating that the patient should not rest the drawing hand or forearm on the table. Attempting to apply this operational definition to patients with MS made the tasks too difficult and in many cases impossible. Therefore the operational definition for the drawing tasks required some modification.

The definitions provided for scoring functional disability (Part C) were found to be misleading for many patients. Many patients with MS have speech difficulties that are not due to tremor, but to the inability to co-ordinate the muscles required for fluent speech resulting in dysarthria. Patients adopt a characteristic monotonous tone with unnatural separation of syllables often referred to as scanning speech. Therefore it was appropriate to assess whether or not the patient presented with a speech problem particularly as dysarthria could present as a side effect of the operation. However the words used to describe the severity of any speech difficulties required that 'voice tremor' be replaced by 'dysarthria'.

In the statements relating to upper limb function the authors have not considered hand dominance nor have they specified which hand is being assessed with regard to the unilateral activities. It is also not clear whether the patient is being asked about his ability to function specifically with his affected hand or whether he is being asked about his overall ability to perform the tasks regardless of which hand he uses.

Patients with the use of one arm only, which may or may not be the dominant arm can learn to feed and care for themselves by learning new tasks. It may therefore

have been more straightforward to assess the upper extremities separately when evaluating the use of the hands for feeding and drinking. The statements provided to score feeding are confusing: one statement suggests the use of one arm only, to bring food to the mouth using a feeding implement; and another statement suggests the use of two arms to cut food using a knife (as we assume a fork is used in the other hand to fix the food that is being cut). Also when assessing the ability to dress the authors include items such as doing up buttons which could be unilateral if the patient adopts a compensatory strategy, with activities which are not possible without the use of both arms, such as tying shoe laces. This is confusing for both the researcher and the patient.

For the purpose of this study and to avoid any confusion we assumed it was the target arm (i.e. the arm contralateral to the side of thalamic stimulation which the DBS was aimed at improving) that was being assessed. Many patients have unilateral movement disorders and are therefore still able to function independently with the non-affected hand although bilateral activities will not be possible. The inability to write legibly will depend on whether or not the movement disorder affects the dominant limb but the statement which evaluates writing ability does not refer to hand dominance. We can only assume that the statement is referring to the ability to write with the dominant hand, which may or may not be disabled by tremor. Despite these weaknesses it was decided to include Part C in the study as it was believed that the outcome in terms of function and the ability to perform activities of daily living is, in a patient's view, more important than reduction or elimination of a symptom such as tremor.

Quantifying functional aspects as in FTRS enables a judgement to be made on the change in functional disability. However the functional activities assessed in FTRS were limited predominately to upper limb function. Patients with MS often have diffuse CNS involvement and therefore scales concerning functional disability should not only assess the specific symptom-orientated improvement of abilities but should also measure the general clinical condition of the patient. Therefore, further evaluation of self care ability (using the self care section of the FIM) and the patients' overall level of ability in performing more general ADL (using the BI) were also established as described elsewhere.

In the original description of the scale the authors recommended that the sub-total scores of Part A, B and C were calculated and then totalled. However, by amalgamating the scores, valuable information about the natural histories and differential behaviour of the components of tremor seen in different parts of the body may be lost. It was therefore decided for this study not to calculate one total score but to calculate total scores for the tremor components (rest, postural, action/intention and goal-related) of each of the body areas.

The scoring form allows assessment of overall severity of tremor-related disability by both the examiner and patient. Attempting to separate the disability caused by tremor from disability caused by other associated impairments such as muscle weakness, spasms, spasticity or sensory loss in patients with profound disability due to advanced MS has its difficulties. Despite this, patients were requested to complete this section at every follow-up visit, and make a subjective judgement of the impact the disorder of movement had on their ability to carry out activities of daily living.

It was anticipated that the subjective self evaluation (at the end of the FTRS form) as to the effectiveness of the intervention made by the patients at every post-operative evaluation would be very useful to monitor the patients' opinion of the effectiveness of thalamic DBS on reducing the severity of tremor over the long term. The patients were asked to make a comparison assessment by scoring their subjective assessment of their current status compared to their last visit. Another advantage of the scale was that it allowed for the patients to carry out a subjective self-evaluation as to the effectiveness of the intervention by asking them to score a comparison assessment at each follow-up assessment (See Appendix 2).

Traditionally, outcome in studies evaluating the effect of surgery for movement disorders in MS has been assessed on clinician-based measures that focus largely on impairment. Recently, there has been greater recognition of the relevance of patients' own perceptions of tremor on their lives (Sandell et al. 1999; Sandell and Thompson 1999). However there is a dearth of information in this area and on the patients' perceptions of changed ability and subjective satisfaction of the outcome after surgery. It was therefore important to address this issue and on initial evaluation it appeared that the FTRS would allow a comparison of the alleviation of the movement disorder to be made between visits, before and after surgery, as well as being useful for determining the effectiveness of thalamic DBS on reducing the severity of tremor.

3.1.2 Modifications made to FTRS for this study

It was necessary to make some minor modifications to the original FTRS for the purposes of this study. The modifications were made to Parts A, B and C of Fahn's TRS and are outlined below. The subjective global assessment and patient's opinion remained as described by Fahn.

3.1.2 (i) Changes to the form

Part A: Some minor modifications and omissions were necessary to the FTRS from its original description in 1988, for its use in the present study with patients with MS. The face, tongue, voice and lower limb tremor were omitted resulting in the assessment of only 4 areas of the body (head, trunk, right upper limb and left upper limb).

Severity of tremor in each of these areas was rated by amplitude but the definitions of the size of the amplitude were modified base on those suggested by Geny (Geny et al. 1996) who devised their tremor amplitude definitions specifically for patients with MDMS: 0 = no tremor; 1 = slight tremor, barely perceivable, maximal amplitude < 1cm, may be intermittent; 2 = moderate tremor, amplitude 1 – 5cm, may be intermittent; 3 = marked tremor, amplitude 5 – 10 cm; 4 = severe tremor, amplitude > 10cm.

The definitions describing postural tremor of the upper limbs were expanded so that the postural tremor elicited with the arms maintained in an extended and a flexed position was assessed in an attempt to separate distal muscles from proximal muscles. Goal-related tremor was assessed separately rather than being grouped with

action/intention tremor. The examiner made a judgement of the severity of goal related tremor after observing the patient perform the seven sub-tests of the Jebsen Test of Hand function (JTHF) (see later in this chapter for a description of the JTHF).

Part B: No changes were made to the wording but a line drawing and a writing task were omitted.

Part C: It was made clear on the form that Part C is an evaluation by the patient of his ability to carry out the tasks with the **target arm** or both (if a bilateral activity). The form was changed with regard to the evaluation of speech, the wording being altered so that voice tremor was replaced by dysarthria. Also the examiner was instructed to complete this section only after referring to the guidelines which gave an explicit explanation of how to complete this section.

3.1.2 (ii) The Modified Fahns Tremor-Rating Scale (MFTRS)

The modifications made to the original FTRS resulted in a modified version that was referred to as the Modified Fahn's Tremor Rating Scale (MFTRS) and is described in summary below (see appendix 4 for sample form for MFTRS).

Part A of the MFTRS included subjective rating of the severity of tremor for the head, trunk, right upper extremity and left upper extremity for (i) rest tremor, (ii) postural tremor elicited with the arms maintained in an extended position and a flexed position, (iii) action/intention tremor and (iv) goal-related tremor. In total this part of the assessment required 18 separate scores (see Table 4-1 of reliability study of MFTRS). For each of these sub-tests or observations the movement disorder was

defined as: 0 = none; 1 = slight, maximal amplitude <1cm; 2 = moderate, amplitude 1 – 5cm; 3 = marked, amplitude 5 – 10 cm; 4 = severe, amplitude > 10cm.

Part B of the Modified FTRS included subjective rating of all the tasks described by the authors, performed with each hand omitting line drawings and hand writing for the reasons described in the sub-section on justification of the methods. These tasks therefore included drawing of Archimedes' spirals (spirography) and pouring water from one cup to another (volumetric test). This part of the MFTRS involved assessment of 6 separate tasks (see Table 4-1).

Part C of the MFTRS assesses functional disability. Its items evaluate the severity of tremor with speaking, eating (feeding), bringing liquids to the mouth, hygienic care, dressing, writing and working including domestic tasks such as homemaking. These scores, with the exception of speaking, are provided by the patients who are asked to evaluate by using the definitions provided below their ability to carry out these tasks using the target arm or both (if a bilateral activity). This part of the FTRS assesses disability in seven aspects of function.

3.1.2 (iii) Revised guidelines

The guidelines although based on those by Fahn *et al*, were expanded. Revised guidelines with explicit operational definitions were set out clarifying how to assess each of the different components of tremor in each of the different areas of the body and the upper limb tasks in a standardized manner to ensure consistency among assessments (See guidelines for completing MFTRS – Appendix 5). Minor

modifications were made to the operational definition for the upper limb tasks in that the patients were permitted to rest their arm on the table whilst performing the tests.

3.1.2 (iv) Revised definitions

The definitions for scoring severity of tremor in Part A were modified (see Definitions for Rating Tremor Severity using the MFTRS – Appendix 6) and set out clearly on a separate sheet along with the definitions assessing functional disability (Part C). A paragraph was added to clarify the role of unilateral activities in Part C in assessing the function of the target extremity, and bilateral activities in assessment of the functioning of both upper limbs.

3.1.2 (v) Revised scoring system

It was decided that calculating the total score would lose valuable information relating to tremor in different areas of the body. Therefore for the purposes of this study it was decided not to calculate one overall total score but to calculate total scores for each of the body areas in Part A. The scores for the different components of tremor in each area of the body were amalgamated. This had an advantage that it allowed a specific evaluation to be made of the target upper limb, which was important for the purpose of this study. Subtotal scores for Parts A (the target upper limb only), B and C were then calculated. Patients with severe movement disorders could potentially score a maximum of 20 for Part A, 12 for Part B and 28 for Part C giving a total possible score of 60 for the upper limb. The percentage severity for the

upper limb was also calculated by expressing the patient's score as a percentage (see Appendix 5 for guidelines on the scoring system).

3.2 Development of a Test of Upper Limb Function for this Study

The JTHF was chosen to measure specific upper limb function in the present study.

3.2.1 Strengths and weaknesses of the JTHF as it related to this study

The JTHF was easy to set up and relatively portable; the equipment needed was readily available at little cost; and the reliability of the JTHF had been established with neurological patients although patients with MDMS were not included in the group.

The only item that needed to be constructed was the test board that was of a simple design. It consisted of a wooden board with a centre ledge made out of a piece of plywood. The centre ledge was offset to the right of the board to allow it to be placed on a 'secretary type desk with a right knee hole'. This presented two minor problems. One was that the wooden ledge did not allow video recording of the patient performing the task as it was necessary to set the video camera up so that it was facing the patient to enable the movement disorder to be seen to its best advantage.

When trying out the JTHF with MS patients with severe movement disorders several points became apparent. Movements of the patients' limbs were often wild and

flailing and it was felt that it would be necessary to fix the board securely to the table. Many of the patients had truncal ataxia with poor trunk control. To overcome this problem it was often necessary to adapt the sitting posture in the wheelchair of many severely ataxic patients. This might involve reclining the back of the wheelchair, using wedge cushions and extending the arm supports to enable the person to be positioned safely in sitting and to be moved from place to place. As a result of these adaptations it was not always possible to position a patient close to the table to enable them to perform the test. Consequently with these patients there was no option but to attempt to perform the functional activities comprising the test from this disadvantageous position. In this situation it was important to position the wheelchair as close to the table as possible. If this was not successful the only other option was to use an electric plinth which could be elevated to accommodate the raised arm rests on the wheelchair.

A trial of the sub-tests with MS patients with mild to severe movement disorders suggested that the JTHF was going to be an appropriate test to use in the study as even patients with severe tremor were able to complete successfully at least one or two of the sub-tests (usually card turning and moving the weighted cans). Also hand function is not an isolated aspect of patient function but is dependent on the proximal part of the upper extremity to position the hand for function. Lack of proximal control is often a significant problem with ataxic patients and they often resort to using a compensatory strategy when attempting to use the arm that involves holding the limb close to the trunk to obtain a degree of fixation. Some of the sub-tests allowed this to occur for example stacking the chequers on the board directly in front

of them. However, others required that the patient reached the arm away from the trunk to successfully perform the sub-test (eg. picking up small objects and placing them into a tin, reaching across the body to lift cans onto the board).

Other factors such as strength, dexterity, sensation, motivation, eyesight, joint mobility, co-ordination needed to be considered as they could also influence the patient's functional ability of the upper limbs. The JTHF not only allowed the impact of the movement disorder on upper limb function to be established but it also permitted identification of those patients with underlying limb dysfunction due to motor and sensory impairments.

Some of the patients took a long time to perform the tests or were unable to successfully complete the subtests. This was a major limitation as the original test only assessed speed of performance of the successfully completed task. It did not allow for patients who might not be able to achieve this. It was therefore apparent that modifications would have to be made to the scoring system of the JTHF for it to be used in this study.

3.2.2 Modifications made to the JTHF for this study

3.2.2 (i) Positioning Of the patient and the test equipment

The patient was seated at a table, preferably a dining table which allowed him to be pushed in close to the table so that the arms of the wheelchair or chair could fit underneath the table. If the patient was wheelchair bound and the arms of the wheelchair did not fit underneath the table the arms were removed for the duration of the assessment. This however was not always possible especially if the patient had

loss of trunk control or severe truncal ataxia which made it dangerous to remove the side supports of the chair. In this situation the chair was pushed as close as possible to the table or if necessary an electric plinth was used as a table and elevated to accommodate the arms of the wheelchair. A note highlighting this necessary modification to the assessment position was made on the assessment sheet to ensure that exactly the same position was adopted for subsequent assessments.

Standardized positioning of the patient in relation to the table and the board was important. The subject's midpoint was taken to be his nose and his midline was an imaginary vertical line through this point The subject was seated with his midline centred on the board when performing the sub-tests that required the use of the board. For the other sub-tests the patient's midline was centred on a fixed marker-point on the table. Markers were fixed to the assessment table to enable the equipment for each sub-test to be laid out in a standardized manner at every evaluation. However in the original article these markers were pieces of tape applied to the edge of the table and it was felt that they therefore did not ensure accurate placement of the equipment. To reduce any error made by the researcher in setting out the equipment specific marker points were used signifying the exact position of the test material on the table. The procedure for setting out the test equipment and the verbal instructions for all seven subtests were standardized as described by Jebsen *et al* (Appendix 8).

3.2.2 (ii) Modifications to the test equipment

The design of the board was modified (see Appendix 9). The board was constructed of perspex rather than wood to overcome the problem of being unable to video record the limb performing the sub-tests The dimensions of the board were also altered slightly so that the board could be placed on top of an ordinary table rather than a desk with a kneehole.

Because many patients with MS had poor fine finger function and were unable to manipulate a ballpoint pen into the correct position so that it was angled to allow it to write, a rollerball felt pen was provided as patients seemed to find it easier to write with. The only other modification was that one side of the cards had a cross marked on them so that there was no doubt as to whether or not the subject had successfully turned the cards over.

3.2.2 (iii) Instructions for performing the sub-tests

To ensure the accuracy of timing and to establish consistency, general instructions were given before each evaluation, asking the subject to prepare for the starting command, to begin immediately, and to work as quickly as possible in a manner in which he would normally perform the activity. The researcher gave the patient the instructions and made sure that they were clear by asking the patient if he understood the instructions. They then instructed the patient to start by saying, '"Ready?" "Go". To record the time required to complete each activity the researcher manually activated a stopwatch simultaneously with the "Go" command to the patient and again at the completion of the task as described by Jebsen (see Appendix 8 for verbal

instructions given to patients). Two minutes was the maximum time allowed to perform each subtest.

3.2.2 (iv) Expansion of the scoring system

It was decided to expand the scoring system (as well as a time score for successful performances) to include a pass or fail score for each subtest. Precise definitions of what resulted in a subject passing or failing a sub-test had to be defined. Guidelines for what constituted a pass/fail and how each test was scored are laid out below.

Test 1:

Pass: the patient can write or print the sentence. The writing must be legible (ie someone who does not know what it is supposed to say must be able to read it).

Fail: if the patient tries but is unable to write e.g. if he cannot hold the pen or if the sentence is illegible.

Test 2

Pass: the patient must turn all cards over. No accuracy of placement is necessary.

Fail: if the patient tries but is unable to pick up the cards, if the patient drops any cards onto the floor or if he is unable to turn all five cards over.

Test 3

Pass: the patient must be able to pick up all six objects in the correct sequence and put them into the coffee can.

Fail: if the patient tries but is unable to pick up all the objects, if the patient drops any of the objects onto the floor or if the coffee can is displaced or knocked over.

Test 4

Pass: the patient must use the spoon to pick up all five beans and put them into the coffee can without knocking it over.

Fail: if the patient tries but is unable to pick up any beans with the spoon, if the patient drops any beans onto the floor, if he cannot hold the spoon, if he cannot pick up and place all five beans into the coffee can or if he displaces the coffee can or knocks it over.

Test 5

Pass: the patient must pick up the chequers (in any order) and stack them one on top of each other, on the board. He is allowed several attempts, i.e. if he knocks them over he can try again as long as no counters fall onto the floor.

Fail: if the patient tries but is unable to pick up the checkers, if the patient drops any chequers onto the floor, if he does not stack all four checkers one on top of each other.

Test 6

Pass: the patient must pick up and place all five empty cans onto the board. If one of the cans is knocked over and it does not roll off the table he may try picking it up again.

Fail: If the patient tries but is unable to pick up the cans or if the patient knocks any cans over and the can rolls onto the floor.

Test 7

Pass: the patient must pick up and place all five heavy cans onto the board. If one of the cans is knocked over and it does not roll off the table he may try picking it up again.

Fail: if the patient tries but is unable to pick up the cans or if the patient knocks any can over and the can rolls onto the floor.

No assistance is to be given to the patient in order to help him perform any of the tests. If the patient drops an object he may pick it up again, if he is able to, as long as it does not fall off the table onto the floor. The time that the patient takes and whether the test is passed or failed is entered on the score sheet (Appendix 10).

CHAPTER 4

VALIDATION OF THE MODIFIED FAHN'S TREMOR RATING SCALE

4.1 Examiner Reliability of the Modified Fahn's Tremor Rating Scale in Patients with Multiple Sclerosis

In order to use the Modified Fahn's Tremor Rating Scale (MFTRS) as a measure of the severity of tremor amplitude to evaluate the effectiveness of thalamic DBS it was essential to determine the applicability of the MFTRS in a cohort of patients with multiple sclerosis. Studies of both the intra-examiner reliability, inter-examiner reliability and validity of the MFTRS in patients with movement disorders due to multiple sclerosis were undertaken (Hooper et al. 1998).

4.1.1 Patients

Ten patients who all fulfilled the criteria for definite MS (Poser et al. 1983) participated in the reliability study. The mean duration of disease was 11 years (range 6 – 19 years). There were three males and seven females; with mean age 40 years (range 31 – 56). All were right handed. Seven were wheelchair bound and the remaining three could walk short distances but had significantly impaired mobility. All of the patients underwent a full neurological examination from which the

expanded disability status scale score (Kurtzke 1983) (EDSS) was obtained. The mean (range) EDSS was 6.5 (4.5 – 8.5). The patients all had severe postural and intentional tremors.

4.1.2 Methods

Video recordings were made of the patients being assessed according to a standardized protocol. The video recording included the following components: 1) 'at rest' in supported sitting and/or supine lying; 2) performing specific purposeful movements such as voluntary movements of the head, drinking from a cup (held by both the examiner and when possible the patient), maintaining the upper limbs in certain positions and performing intentional movements and the finger/nose test; 3) attempting to sit unsupported for 60 seconds; stand unsupported for 10 seconds; and walk 10 metres; 4) performing spirography described above; 5) performing a volumetric test (the operational definitions for these tests being described in detail in Chapter 2 where Part B of FTRS is described); and 6) performing hand writing and card turning from the Jebsen Test of Hand Function (Jebsen et al. 1969) (JTHF). A composite and edited video of all 10 patients performing these tasks was compiled and distributed to each examiner (described below) who used the scale as follows.

The MFTRS comprises three parts, A, B and C as discussed earlier. Part C assesses functional disability as scored by the patient and consequently is not included in this reliability study. In total 24 separate scores, 18 for Part A and 6 for Part B were obtained for each patient (See Table 4-1).

4.1.3 Assessment of the patients

For the intra-examiner assessment one examiner (JH) rated the 10 patients on each of the 24 tests on two separate occasions, 3 months apart. For the inter-examiner assessment eight examiners (3 medical practitioners and 5 physiotherapists) were approached (Appendix 12) and issued with copies of the scoring guidelines (see Appendix 5), definitions of tremor severity (Appendix 6), scoring sheets (see Appendix 13) and instructions for the examiners (see Appendix 14). The examiners were asked to familiarize themselves with all of these. They were then asked to watch the videotape of the 10 patients and to rate each patient's tremor on each of the 24 tests.

Six of the examiners worked in clinical neurosciences in different units within Edinburgh and two of the examiners were Physiotherapy lecturers involved in teaching neurology at under-graduate and post-graduate level. None of the examiners had any experience before the study using either the original Fahn's Tremor Rating Scale or the modified version that was being evaluated. All ratings were performed independently.

4.1.4 Statistical analysis

Non-parametric statistics were used throughout. Intra-examiner reliability (somewhat analogous to test-retest reliability) data were analysed using Spearman correlations and Wilcoxon matched-pairs signed rank tests. Data on inter-examiner reliability were analysed using Kendall's Coefficient of Concordance (from which average

inter-examiner Spearman correlations can be derived) and Friedman Analysis of Variance. Statistical calculations were performed using SPSS for Windows.

4.1.5 Results

All examiners completed the requisite assessments and did not comment upon any particular difficulties. Once the examiners had familiarized themselves with the scale it was found to be easy to use and tremor was rapidly assessable.

4.1.5 (i) Intra-examiner reliability

The intra-examiner reliability coefficients (Spearman correlation coefficients (r_s)) are shown in Table 4-1; and range from 0.85 – 0.97 for the different categories of head tremor, 0.64 – 0.93 for trunk tremor, 0.92 – 0.99 for the right upper limb tremor, 0.81 – 0.99 for the left upper limb tremor and 0.87 – 1 for the tremor evident when performing upper limb tasks (spirography and volumetric test). Levels of reliability were high except when certain categories of tremor in the trunk were assessed (postural tremor $r_s = 0.64$ and goal related $r_s = 0.72$).

Correlations could not be computed for rest tremor of any of the four body parts because nearly all patients received identical ratings of 0, indicating that rest tremor was not present in these patients with MS.

The Wilcoxon matched pairs signed rank tests showed no significant differences (p values all > 0.05) between the level of ratings of tremor on any of the 24 measures when rated by the same rater on two different occasions 3 months apart, indicating that there was no 'drift' to more stringent or more lenient rating (Table 4-1).

4.1.5 (ii) Inter-examiner reliability

The average value of the Spearman correlations between all possible pairs of examiners was calculated by Kendall's Coefficient of Concordance to determine the overall agreement for each measure among the 8 examiners' sets of scores. The inter-examiner reliability coefficients range from 0.69 – 0.99. The scores for rest tremor, where nearly all ratings on these measures were zero ranged from 0.01 – 0.28, confirming the absence of rest tremor in this patient sample.

Friedman Analysis of Variance was used to establish whether some examiners scored patients more strictly or more leniently than did other examiners. Results in Table 4-1 show a number of significant differences in the rating levels (those with p values <0.05) indicating that although there was good agreement amongst examiners as regards the ranking of the severity of tremor in different patients, examiners varied in their interpretation of the severity of tremor required for allocation to given points on the 0 to 4 scale. Subsequent analysis showed that the two non-medically qualified academic examiners, who are not in regular clinical practice, tended to rate tremor as more severe than did the medical staff and the physiotherapists, working in clinical neuroscience practise within the NHS, who tended to differ little amongst themselves.

Table 4-1: Intra-examiner and inter-examiner reliability of the Modified Fahn's tremor rating scale

Rating of Tremor	Intra-examiner reliability		Inter-examiner reliability	
	Spearman correlation coefficient	**Wilcoxon matched pairs signed ranks test (p value)**	**average Spearman* correlation coefficient**	**Freidman ANOVA (p value)**
HEAD TREMOR				
1.Rest	not computed	1	0.28	0.002
2.Postural	0.92	0.56	0.87	0.004
3.Kinetic/Intention	0.97	0.32	0.82	0.001
4.Goal	0.85	0.41	0.77	0.002
TRUNK TREMOR				
5. Rest	not computed	1	0.01	0.02
6. Postural	0.64	1	0.84	0.166
7. Kinetic/Intention	0.93	0.16	0.76	0.001
8.Goal	0.72	0.68	0.72	0.008
RIGHT UPPER LIMB				
9.Rest	not computed	1	0.22	0.001
10. Postural a)	0.99	0.16	0.87	0.009
11.Postural b)	0.99	0.32	0.86	0.489
12. Kinetic/Intention	0.92	1	0.87	0.001
13. goal	0.94	0.16	0.84	0.009
LEFT UPPER LIMB				
14. Rest	not computed	1	0.19	0.001
15. Postural a)	0.94	1	0.86	0.001
16. Postural b)	0.99	0.32	0.9	0.005
17. Kinetic/Intention	0.93	1	0.73	0.001
18. Goal	0.81	0.66	0.69	0.003
Upper LIMB TASKS				
19. Large spiral-right	1	1	0.93	0.005
20. Large spiral-left	0.99	0.32	0.81	0.232
21. Small spiral-right	1	1	0.93	0.292
22. Small spiral-left	0.87	0.16	0.92	0.912
23. Pouring-right	1	1	0.97	0.195
24. Pouring-left	0.99	1	0.99	0.333

* derived from Kendall's coefficient of concordance

4.2 Validity Of The Modified Fahn's Tremor Rating Scale

The MFTRS has high face validity. Aspects of its validity were assessed by calculating the correlation coefficients between the ratings of tremor in the MFTRS, the spiral tests (large and small), the volumetric test (pouring water) and the total number of passes on the Jebsen test of hand function using data collected at the pre-operative assessment in 32 patients with MS (Table 4-2). Correlations between the different components of tremor within the MFTRS (excluding rest tremor) ranged from 0.58 to 0.94 and correlations between the ratings for the different components of tremor and the number of passes on Jebsen THF ranged from 0.37 to 0.63. The ratings of the different components of tremor correlated between 0.42 and 0.64 with performance on large spirals and between 0.43 and 0.88 with performance on the pouring test. However correlations with the performance on the small spiral drawing ranged only from 0.30 to 0.51. These correlations provide evidence for the validity of these tests in the assessment of tremor.

The concurrent validity of the MFTRS was further assessed by calculating the correlation coefficients between the different component parts of the MFTRS and measures of impairment, disability and handicap (Table 4-3).

There was moderate to good correlation, ranging from 0.53 to 0.75, between all the components of the MFTRS (except the large spiral) and the cerebellar functional system score of the Kurtzke, providing further evidence of validity in that the tremor

scored by a neurologist on clinical examination correlates with tremor scored on the MFTRS.

Table 4-2: Correlations (Spearman's rho) between the different ratings of tremor, spiral tests, volumetric test and the total number of passes on the JTHF. N of cases = 32

	Rest trem	Post a) trem	Post b) trem	Kin/int trem	Goal trem	total score	Large spiral	Small spiral	Pour water
Total passes JTHF	0.12	-0.37*	-0.48**	-0.63**	-0.51**	-0.55**	-0.74**	-0.79**	-0.41*
Rest trem		-0.08	-0.04	0.02	-0.05	0.01	0.13	0.10	0.80
Post a) trem			0.73**	0.64**	0.58**	0.84**	0.42*	0.30	0.43*
Post b) trem				0.78**	0.83**	0.94**	0.42*	0.40*	0.64**
Kin/int trem					0.83**	0.90**	0.64**	0.51**	0.74**
Goal trem						0.90**	0.50**	0.42*	0.88**
Total trem							0.55**	0.45*	0.74**
Large spiral								0.9**	0.43**
Small spiral									0.34

*correlation is significant at the 0.01 level (2-tailed)
** correlation is significant at the 0.01 level (2-tailed)

Table 4-3:Correlations (Spearman's rho) between the different component parts of the modified Fahn's TRS and other measures of impairment, disability and handicap. N of cases =32

	Post a)	Post b)	Kin/int	Goal	Total	Large	Small
JTHF	0.29	-0.13	-0.42	-0.53	-0.80	-0.36	-0.58
LHS	0.27	0.04	-0.10	0.17	0.15	0.35	0.08
FSS	-0.48	-0.10	-0.20	0.35	-0.25	0.25	0.36
FIM	0.13	-0.19	-0.24	-0.09	-0.09	0.12	0.13
CBFS	0.12	0.75*	0.71*	0.56	0.56	0.29	0.53
HAD	-0.17	0.32	0.02	0.36	0.10	-0.24	0.12
HQ	0.21	-0.21	-0.08	0.09	0.03	0.31	0.16
EDSS	-0.30	0.12	0.07	0.09	0.04	-0.11	-0.04

*Correlation is significant at the 0.05 level (2-tailed)

Legend for Tables 4-2 and 4-3: The abbreviations in the first rows of the tables relate to the different components of tremor of the target arm where: Rest = rest tremor, Post a) = postural tremor when the arm is maintained in an extended position, Post b) = postural tremor when the arm is held in a flexed position, kin/int = Kinetic/intention tremor, Goal = goal related tremor, Total = total tremor score for the upper limb, Large = drawing of large spiral and Small = drawing of a small spiral, Pour water = a volumetric test involving pouring water from one cup to another.

The abbreviations in the first column of table 4-3 relate to the measures of impairment, disability and handicap where: JTHF = Jebsen Test of Hand Function, LHS = London Handicap Scale, FSS = Fatigue Severity Scale, FIM = Functional Independence Measure, CBFS = Cerebellar Functional System of the Kurtzke Functional Systems Scale, HAD = Hospital Anxiety and Depression Scale, HQ = Handicap Questionnaire, EDSS = Expanded Disability status Scale.

CHAPTER 5

DESIGN OF THE STUDY AND ASSESSMENT OF EFFICACY OF THALAMIC DBS

5.1 Selection of Patients

5.1.1 Referral of patients

Patients with medically refractory and disabling movement disorders were referred by their general practitioners or neurologists to the Department of Clinical Neurosciences (DCN) at the Western General Hospital in Edinburgh for assessment and inclusion in the study. They were therefore an incidental sample. The neurologists within Lothian region were aware of this study and were issued with detailed patient information sheets (Appendix 23) to inform suitable patients about the study. There was a waiting list of patients with severe movement disorders due to MS who were prepared to be assessed and to be considered for thalamic DBS, if after extensive evaluation they were deemed suitable candidates.

5.1.2 Criteria for inclusion

Criteria for inclusion in this study were adult patients :

a) with an established diagnosis of MS (Poser et al. 1983) with a movement disorder causing significant functional disability

b) in whom unilateral or bilateral severe tremor of the upper limbs had been present for at least six months and which was deemed disabling by the patient and the research team

c) in whom a neurologist had determined that the patient's movement disorder could not be controlled adequately by medications

d) who were able to give informed consent

e) who were available for appropriate follow-up times throughout the length of the study.

5.1.3. Criteria for exclusion

Were:

a) severe sensory-motor disability in the tremulous limb

b) major cognitive dysfunction such that QOL was unlikely to be altered by resolution of the movement disorder.

5.1.4 Aims of surgery in patients selected for the study

Patients with severe upper limb movement disorders that caused a major functional deficit and in whom it was considered there was potential for improvement were selected. After the initial assessment of each individual patient the target upper limb was identified for treatment.

5.1.5 Initial pre-operative consultation

Most patients were assessed initially in the outpatient clinic by the consultant neurosurgeon to determine their suitability for the study and the probable target upper limb. During this initial consultation the history was taken, a 'screening' neurological examination was performed, the nature and aims of the study outlined, and the need for more comprehensive clinical assessment emphasized. Some patients were excluded from further assessment after initial consultation, since their poor clinical and /or cognitive status precluded the likelihood of any useful amelioration of the functional condition by thalamic DBS. Those patients considered 'possible' candidates for the study were later subjected to intensive clinical examination, neuropsychological assessment and video recording; and confirmation of the target arm.

5.2 Patient Consent

Patients who met the criteria for admission and were considered appropriate candidates for DBS after extensive assessments were given a detailed patient information sheet about the nature of the study (Appendix 23). A standardized consent form was signed by patients to acknowledge their agreement to participate in the study (Appendix 24) and for visual records to be taken (Appendix 25) and an entry form was completed by the neurosurgeon (Appendix 26). Where the movement disorder precluded signing of the consent form a close relative was asked to sign instead. The study was approved by the Lothian Health Board Ethics Committee.

5.3 Design of the Study

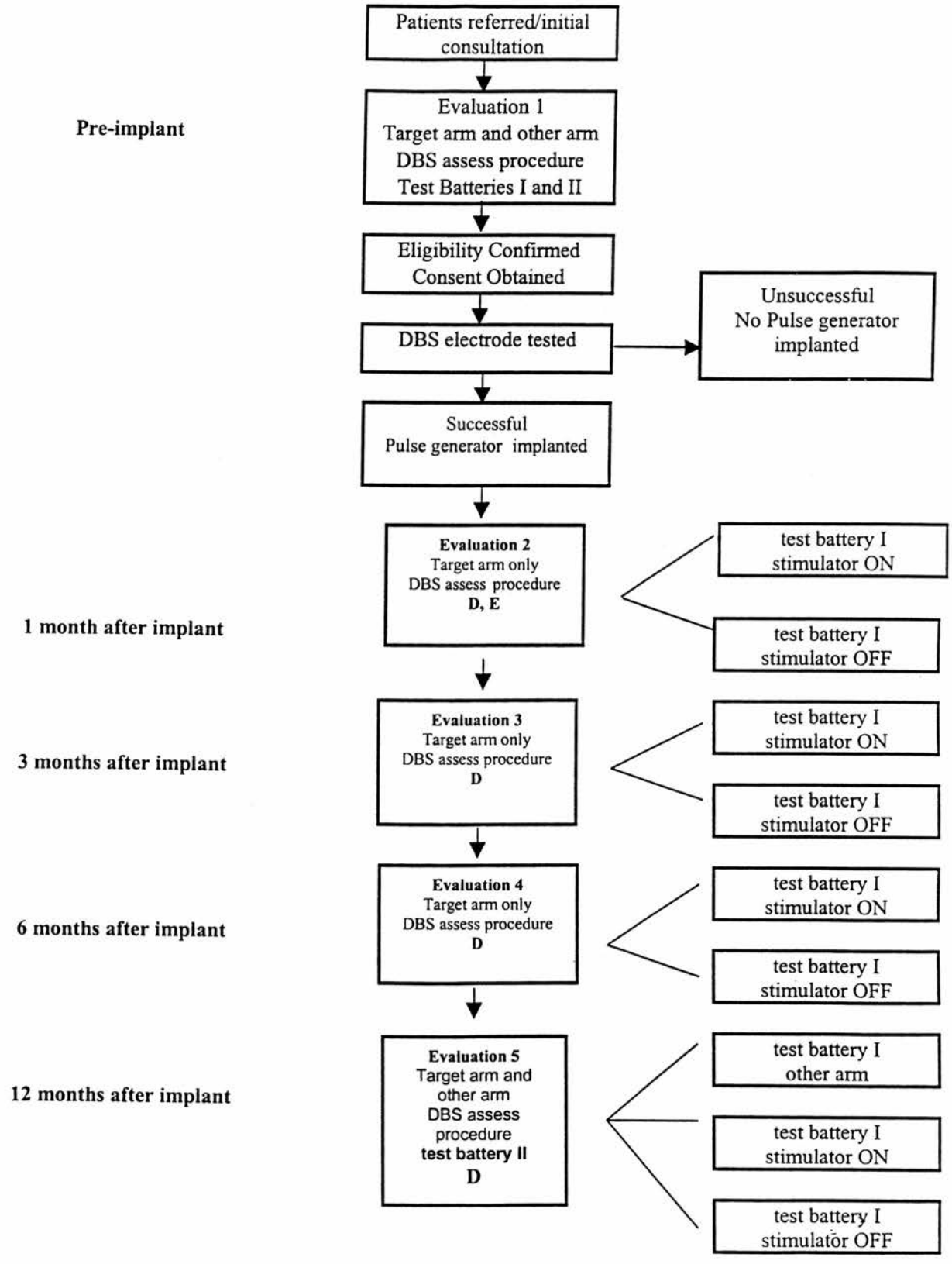
The design of the trial was a prospective, same-subject design involving patients with MS. Each subject served as his or her own control since the thalamic DBS could be turned on and off. MS subjects were tested extensively preoperatively over a two day period at the Astley Ainslie Hospital whilst the patients were in-patients in the neurorehabilitation wards for an overnight stay. This enabled the patient's level of functional independence to be observed whilst staying on the ward. It also enabled the patients to relax and have rest periods if required, lying down between the assessments. This was felt to be important in view of the fact that many of the patients were easily fatigued.

Where possible an interview was carried out with the patient and his main carer so that levels of independence in the home environment could be established.

Postoperative evaluations were carried out during day admission to the Astley Ainslie Hospital so that reassessments could be performed by the researcher in the morning and by the doctor in the afternoon after the patient had eaten lunch and had a rest. The post-operative evaluations (apart from the 12 month evaluation) took less time to complete than the initial pre-operative evaluation as they involved performing fewer tests (test battery I only- see section 5.4.1 (i)). Only the target arm was evaluated at one month, three months and six months post-operatively but at twelve months both the target arm and the other arm were evaluated. Test battery II (see section 5.4.1 (ii)) was also repeated at this time.

Two identical evaluations (involving completing test battery I twice) were performed post-operatively on the target arm of each patient, one with the thalamic stimulator switched on and the other with the thalamic stimulator switched off. The assessments were carried out in the sequence shown in Figure 5-1; the evaluations were performed in random order (see randomisation of assessment sheet in Appendix 26) to minimize practice effects and the researcher was blind with respect to the on/off status of the stimulator (ie. to the order of the assessments). It was not possible for the patients to be blind to stimulator status as some of them experienced a 'kicking in' effect when their stimulator was turned on.

Figure 5-1: Diagram showing trial design of study patients with MS referred for thalamic DBS



ASSESSMENTS

A = Fahn's Tremor Rating Scale
B = Jebsen Test of Hand Function
C = sitt/stand/10m walk

D = Kurtzke EDSS
E = Neuropsychology

F = Functional Independance Measure
G = hospital Anxiety and Depession Scale
H = Handicap Questionnaire
I = London Handicap scale
J = Fatigue severity Scale

Test battery I = A, B, C

Test battery II = F, G, H, I, J

5.3.1 Procedure for 'blinding' the researcher

Before starting the assessments at each post-operative evaluation the researcher asked a member of the nursing staff on the ward to help with the study by setting the stimulator to the mode shown on the Patient Assessment Randomization Sheet (Appendix 27). These sheets were compiled by the statistician in the Department of Clinical Neurosciences and given to the researcher in a sealed envelope.

First, the researcher demonstrated to the nurse how to turn the stimulator on and off using the programming console. The nurse then followed written instructions (see Appendix 28) to put the stimulator into the correct mode for the first assessment This was done once the researcher had left the room to ensure that she was not aware of whether the thalamic DBS had been switched on or off. The first assessment was then carried out and the nurse was then asked to follow the instructions written on the randomization sheet for the second assessment and change the setting of the stimulator accordingly. Once again the researcher left the room while this took place.

5.4 The Clinical Evaluations

5.4.1 Tests comprising the test series

The complete series of tests comprised test battery I, test battery II, scoring of the Kurtzke EDSS and a neuropsychological assessment. The various scales and tests which compiled the test batteries have already been listed in this chapter and were described earlier in Chapter 2.

5.4.1 (i) Test Battery I

Test battery I comprised the primary outcome measures for the study. The assessments in test battery I covered three main areas:

1. Assessment of the disorder of movement (tremor/ataxia) using the Modified Fahn's Tremor Rating Scale.

2. Assessment of upper limb function using the Jebsen Test of Hand Function

3. Assessment of truncal and lower limb involvement using protocols for sitting, standing and walking 10 metres.

Test battery I was carried out at every evaluation during the study.

5.4.1 (ii) Test Battery II

Additional information, comprising Test battery II was also collected at two time intervals during the study, at the pre-operative evaluation and again at 12 months after operation. Test battery II comprised of subjective scales. The self-care section of the Functional Independence Measure (FIM) was completed by the researcher. The other scales, the London Handicap Scale, the Hospital Anxiety and Depression Scale, the Fatigue Severity Scale, the Handicap Questionnaire and the assessment of the patient's opinion of the operation were all completed on the basis of the patient's own report.

5.4.1 (iii) Neurological Assessment

A member of the medical team also completed a full neurological assessment at the preoperative assessment and at the 12 month assessment and the Kurtzke EDDS was subsequently scored for each assessment.

5.4.1 (iv) Neuropsychological Assessment

The neuropsychologist in the Department of Clinical Neurosciences performed a brief neuropsychological assessment preoperatively and again at one month after operation.

5.4.2 Sequence of the performance of the tests

The tests were always performed in the sequence shown in figure 5-2.

Fig 5-2: The sequence of the performance of the tests

First Day- TEST BATTERY I

Assessor rated the patient's:

1. tremor – using the modified Fahn's Tremor Rating Scale
2. drawing of spirals
3. pouring of water from a cup
4. sitting for 1 minute
5. standing for 10 seconds
6. walking 10 metres

Patient was given a 15 minute rest

Assessor scored and timed the patient performing:

7. subtests of the Jebsen Test of Hand Function

(The above assessments were performed first with the probable **target arm** and then with the **other arm**)

Patient was asked to :

9. score the ADL questions in the modified Fahn's TRS.

Assessor and **patient**:

10. provided an overall, complete rating of the effect of tremor on disability

End of researcher's evaluation. Patient was given lunch and time to rest

Neurologist carried out a full Neurological Assessment (to include Kurtzke's EDSS).

Second Day- TEST BATTERY II

Assessor scored the patient's level of functional ability using:

1. the Functional Independence Measure

Patient completed the:

2. London Handicap Scale
3. Hospital Anxiety & Depression Scale
4. Fatigue Severity Scale
5. Handicap Questionnaire

End of researcher's evaluation. The patient was given a long rest

Neuropsychologist carried out the neuropsychology assessment.

5.4.3 Video protocol of the tests

The assessments of Test Battery I were carried out by the researcher in a predetermined sequence and a video recording was made of the patient performing the tests.

Fig 5-3: The video protocol of Test Battery I and the requests made of the patient by the researcher

1) **Patient sitting on chair, with forearms lying on thighs** 30s

*Patient asked to move head and look to the right, left, up and down

* Patient asked to move head and take a drink from a cup with a straw, held stationary by the examiner.

Speaking:

* Ask patient to tell his or her history of the disease.

2) **Posture holding:**

* Arms outstretched, wrists slightly extended, fingers abducted..... 15s

* Arms held with elbows flexed, shoulder abducted and fingers spread apart, index fingers opposed at level of the chin 15s

3) **During Action**

* Finger to nose, three times each side 15s

4) **Drawings:**

* Fahn's rating scale for tremor, 2 spirals

Test each hand 60s

5) **Pouring:**

* Fahn's rating scale for tremor. Ask patient to pour water from one cup to another. Test each hand separately 30s

6) **Patient lying supine:** 30s

7) Sitting unsupported on plinth for 1 min .....1 min

8) Arising from a chair and standing for 10 secs 15s

9) Gait

* 10 metre walking test

The patient is then given a 15 minutes rest before performing other goal specific tasks:-

10) Jebsen Hand Test:

7 Subtests

Each test is performed first with the non-dominant

hand and then with the dominant hand 20mins

5.4.4. Clinical grading of the various components of tremor

The clinical grading of the various components of tremor was performed in the following way: the rest component of head tremor was assessed with the patient lying flat on the bed, with the head supported by pillows, and the postural component whilst the patient was sitting without head support looking straight ahead. The upper limbs were also assessed with the patient sitting. The rest component of tremor was scored whilst the arms were relaxed and totally supported in the patient's lap and the postural component whilst the arm were first held out in front, with the hands pronated and the fingers spread apart (postural a)) and then secondly when the arms were maintained with the elbows flexed and the forefingers near but not touching the nose (postural b)). The kinetic/intention component was measured as the subject's

index finger approached a target during the finger nose test. The examiners finger was placed at the limit of reach.

Detailed operational definitions for carrying out the tests 1 – 3 in test battery I are provided in Appendix 6 (Definitions for the clinical grading of the various components of tremor using the MFTRS) and Appendix 5 (Guidelines for completing the MFTRS). Results were recorded on the Modified Fahn's Tremor Rating Scale scoring form (Appendix 4)

5.4.5 Clinical assessment of the functional tests

The standardized protocols for performance and assessment of tests 4 – 6 are provided in Appendix 5. Results were recorded on the same sheet (Appendix 4).

Detailed operational definitions for were set out for the JTHF in Appendix 8 and included information on: the specification for placement of the test equipment and the subject; the equipment required and standardised procedures and instructions for completion and assessment of the subtests of the JTHF. The results were recorded on the 'Jebsen Hand Test-pre-operative assessment form' (Appendix 10) at the pre-operative assessment and at subsequent reassessment after implantation of the thalamic DBS the 'Jebsen Hand Test-post-operative assessment form' (Appendix 11) was used.

5.4.6 Test environment

Because concentration was required the assessments were carried out in a quiet room on the ward. This enabled the same table and chair to be used for the upper limb

tasks although if the patient was confined to a wheelchair he remained seated in it for the duration of the assessments. The only assessment that was not performed in the room was the timed 10 metre walk test. This was carried out at the far end of the ward where fixed, standardized markers had been placed on the floor.

5.5 Implantation And Programming Of The Thalamic Deep Brain Stimulator And Pulse Generator.

5.5.1 Neuroradiological investigations

Each patient had a cranial magnetic resonance imaging (MRI) scan performed prior to the surgery to enable the width of the third ventricle, the thalamus and capsule to be measured and the presence of atrophy, ventriculomegaly, location and number of plaques to be determined.

5.5.2 Thalamic DBS implantation

Implantation of the thalamic DBS took place in two stages.

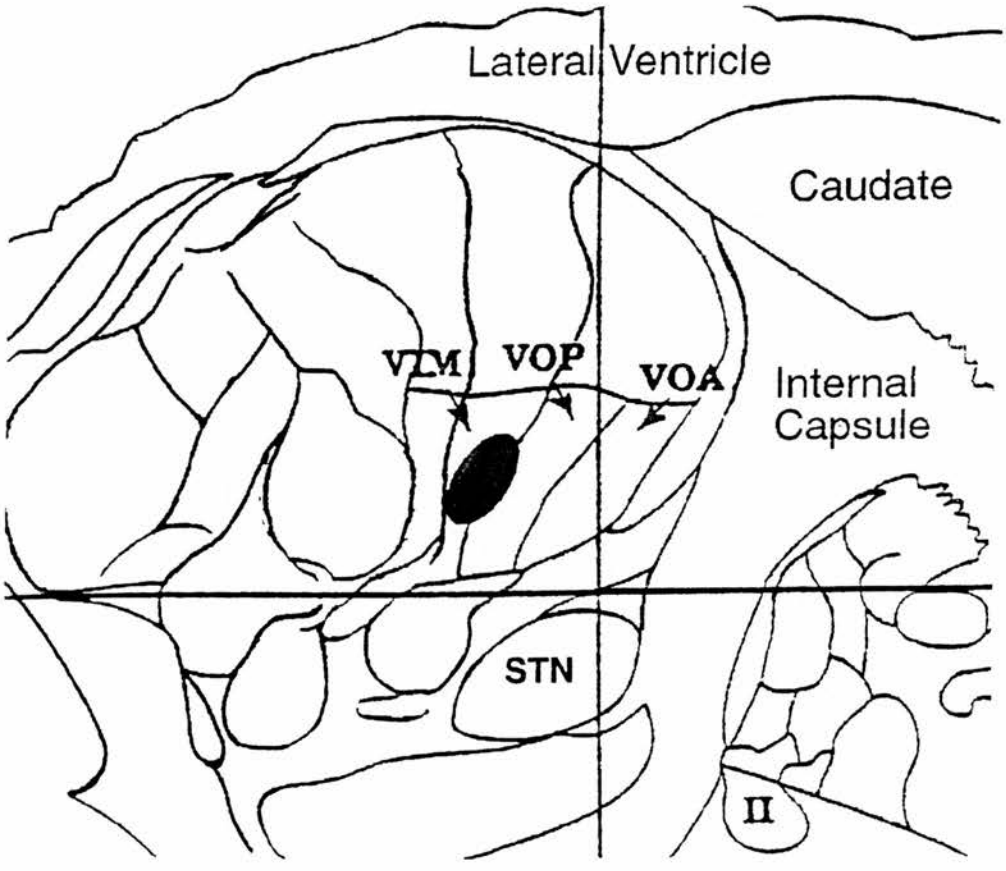
5.5.2 (i) Stage 1: Neurophysiological exploration of the thalamus and implantation of the DBS lead

Patients were given a general anaesthetic using propofol infusions and the stereotactic headframe was affixed. The pin sites were infiltrated with local anaesthetic. A coronal burrhole was drilled, the dura opened, and the wound loosely closed. The Brown-Robert-Wells (BRW) computerized tomography (CT) localizer

system was then fitted to the base ring and a BRW CT performed to localize the anterior commissure (AC) and posterior commissure (PC). Once the appropriate CT gantry tilt was obtained the AC-PC plane was identified and the fiducial, AC, PC co-ordinates obtained. Targets were selected beginning 1mm behind the AC-PC midpoint and between 11 – 15 mm lateral to the midline. The stereotactic co-ordinates were calculated.

The patient was returned to theatre, the propofol infusion stopped, the burrhole wound opened and the entry point obtained for insertion of the electrode. A Guildenberg stimulating electrode was then passed towards the target, once the patient was awake and co-operative. Stimulation began 5mm short of the target. The electrode was advanced in 2mm steps with low (2Hz), intermediate (20Hz) and high frequency (100Hz) stimulation at each locus. Effects on motor and sensory function, eye movements, language and articulation were assessed. The ideal point for electrode insertion was that at which stimulation at 1.5 – 2.0 V produced suppression of tremor with no neurophysiological side effects. The DBS lead was then implanted via a cannula at this site. The deepest DBS electrode was implanted 1mm deep to this site so that the 4 electrodes straddled the region of maximal suppression of tremor. A burr hole ring and cap was used to stabilize the lead on the cranium. An external stimulating lead was then connected to the DBS electrode, tunnelled subcutaneously and brought out above the ear. This enabled a period of testing of the efficacy of the DBS to be carried out in the ward. Information regarding the first stage of the procedure was recorded on the 'Lead Implant Data Collection' form (Appendix 29).

Figure 5-4: Location of the target site for DBS in the ventrolateral nucleus of the thalamus



This is the site of stimulation most commonly used for ameliorating tremor. The horizontal axis is that of a horizontal plane drawn at the AC-PC line. The vertical axis represents a horizontal plane drawn through the midpoint of the AC-PC line. VOA, ventralis oralis anterior; VOP, ventralis oralis posterior; STN, subthalamic nucleus; II, cranial nerve II. Figure taken from Atlas for Stereotaxy of the Human Brain (Schaltenbrand and Wahren 1977).

Initial testing and assessment of microthalamotomy effect

Some patients experienced a 'micro thalamotomy' effect due to lead implantation, which resulted in immediate suppression of tremor. This effect usually waned in the first weeks after surgery and it was sometimes necessary to delay stage two of the procedure until tremor reappeared. However, in most cases, tremor became evident a few days after the first stage of the procedure and the patient was tested using an Itrel Screener (a temporary external power source used to test the effect of the stimulation) to confirm persistent suppression with appropriate thalamic stimulation.

5.5.2 (ii) Stage 2: Implantation of the IPG

Between five and seven days later, with the patient under general anaesthesia, the Itrel II IPG was placed subcutaneuosly in the subclavicular region. The IPG was left in the off position. An extension wire was connected to the lead and threaded subcutaneously to pass caudally behind the ear, down the neck, and it was then connected to the IPG. Information regarding stage 2 of the procedure was recorded on the 'IPG Internalization' form (Appendix 30).

5.5.2 (iii) Justification of the surgical methods

Until recently, thalamotomy was the only technique which could be used to treat tremor refractory to medical treatment (Nguyen et al. 1996). However, despite the relief of tremor afforded in the short term by thalamotomy to suppress MDMS its use remains controversial. There are reservations regarding the thalamotomy operation first because of the residual ataxia and secondly because of the high risk of serious complications, particularly if thalamotomy is performed bilaterally, as the procedure

is irreversible. One of the main reasons for the limitation of the use of thalamotomy is the reluctance to cause permanent lesions of the CNS (Geny 1996). Continuous stimulation of deep brain structures in the treatment of disorders of movement is an attractive method of avoiding permanent side effects which can follow a stereotactic localized destruction.

Long term thalamic DBS and thalamotomy have the same co-ordinates of the surgical target and the improvements of tremor in MS seem the same in the short term but it has the advantage of being reversible and adjustable and the morbidity appears less (Geny et al. 1996; Schuurman et al. 2000).

5.5.3 Initial IPG programming

IPG programming was performed 24 hours after operation when the complete DBS system had been implanted. For the purpose of programming the device, the Itrel Console Programmer was used to select parameters of stimulation that provided the greatest degree of suppression of tremor with the least side effects. Adjustable parameters included amplitude of stimulation (intensity of the stimulation signal), pulse duration and rate, and selection of electrodes and their polarity. All four electrodes could be selected to be negative or positive polarity, or off. The IPG case could be assigned a positive polarity or off. At least one negative and one positive contact (electrode or IPG case) were required to complete the electrical circuit.

The neurosurgeon (IRW) and the researcher (JH) made all programme adjustments. The recommendations made by Medtronic (amplitude < 3V, pulse width 60μs, rate 130 – 185Hz) were followed at the initial setting of the programmable parameters but

the preference of electrode setting depended on the exact location of the DBS electrode in the thalamus. Verification of these initial settings was made ad hoc and then adjustment of the parameters of stimulation was performed as needed for optimum tremor suppression.

There were two amplitude settings available for programming: the normally programmed amplitude setting and the magnet amplitude setting. Both features are necessary if the patient is required to switch from one amplitude setting to another as required when the system is used as a dorsal column stimulator to relieve pain. However for the purposes of this study, where the stimulator was used to stimulate the thalamus, this was not necessary. The researcher therefore always set the magnet amplitude to be equal to the normally programmed amplitude. The final stimulation parameters were recorded on the 'Stimulation IPG Parameters' form (Appendix 31).

5.5.4 Education of the patient and carer

The patients were provided with a control magnet and they and their carers were instructed in its use: the patient could then turn the stimulator on and off by placing the hand held control magnet over the IPG for a few seconds (Appendix 32). All patients were instructed to turn the stimulator off before retiring each night to extend the IPG battery cell life. Readjustments of the IPG parameters were made as needed during scheduled study visits or during interim visits if loss of benefit developed. Either the patient attended the hospital for this or the researcher visited the patient at his home.

The patient was also given an information booklet produced by Medtronic, outlining some important aspects of the thalamic DBS. Patients were cautioned about potential hazards such as theft control devices. They were also issued with an identification card to carry with them at all times listing the serial numbers of the implanted components and an emergency contact number at the Department of Clinical Neurosciences.

5.6 Other information Collected at the Post-operative Follow-Up Evaluations

5.6.1 Alterations to the stimulation parameters

It was often necessary to make minor adjustments to the parameters of stimulation to obtain an optimum effect. This was always recorded (see Appendix 33 for 'Follow-up' form).

5.6.2 Assessment of adverse effects

Safety information was recorded throughout the study on standardized case report forms (See Appendices 34 & 35 for 'Therapy Adverse Events' and 'Systems Complications' forms). Information regarding the severity, duration, and suspected aetiology of any reported complications or adverse effect was collected, and any intervention recorded. Whether the adverse effect was observed with and or without

electrical stimulation was also noted. All complications and adverse effects were recorded on the case report form as soon as they were known.

5.6.3 Assessment of patient's ability to turn the stimulator on and off

In the immediate post-operative period some patients had difficulties turning the stimulator on and off using the hand held magnet supplied for this purpose. Therefore at every subsequent evaluation they were asked who was responsible for turning the stimulator on and off in the morning and evening (Appendix 36).

5.7 Health Economic Measurement of the Cost Benefit of Thalamic DBS

5.7.1 Methods used to assess the related costs

5.7.1 (i) The costs involved in assessing the patient

The patients were referred to the neurosurgeon for their suitability for implantation of a thalamic DBS to be assessed. The patient was then seen as an outpatient, for an initial consultation in the outpatient clinic of the Department of Clinical Neurosciences. If deemed an appropriate candidate they were then admitted at a later date to the Astley Ainslie Hospital so that extensive baseline assessments could be carried out. These assessments were carried out over a two-day period, which necessitated an overnight stay on the rehabilitation ward.

This was an experimental study and it was not possible to recruit adequate numbers of MS patients with movement disorders from Lothian region for the study. Patients living elsewhere were therefore also accepted. However to determine whether or not they were appropriate candidates it was necessary that they came to Edinburgh for the pre-operative assessment. In all cases, even for patients living in Edinburgh, they were admitted for an overnight stay to enable the pre-operative evaluation to take place over two days. In cases where the patients lived a considerable distance form Edinburgh, the neurosurgeon also saw the patient whilst they were in the ward at Astley Ainslie Hospital, rather than seeing them initially in the outpatient clinic, which was the procedure for patients living more locally. The relevant costs involved in the initial assessment stage of each patient were calculated from costs provided by the local Trust providers.

5.7.1 (ii) The costs involved in implanting the thalamic DBS

Prices were calculated for operations as an average charge (average specialist tariff). In calculating this average charge several factors are taken into account. These were the type of operation (each operation having a procedure code), the average length of stay for that particular operation, consumables utilized (syringes, food, drugs), staff salaries and time and overheads incurred by the unit. Thalamic DBS was a new technique and was being performed in only a small number of cases so the Finance Department included it under the code for stereotactic operations.

The Western General Hospital NHS Trust had a contract with Lothian Health Board to treat patients within Lothian at a contract cost. Patients were also referred to the

study from outwith Lothian. For these patients although the resource use was the same, the cost of the procedure was higher as they were charged an Extra Contractual Referral Rate (ECR). Authorization for ECRs had to be sought from the referring Health Authority by the Contracts and Planning Department before the procedure could be carried out.

It became apparent that some of the patients required a short period of intensive training of their target upper limb after the operation. This was organized on an in-patient basis in the majority of cases at the Astley Ainslie Hospital. However some patients required more intensive rehabilitation to return to their preoperative level of functional ability in addition to intensive retraining of the target upper limb. The researcher often had to make frequent visits to the rehabilitation hospitals during the first month after the operation as it was often necessary to carry out some 'fine tuning' of the patient's thalamic DBS using the Itrel Console Programmer. This involved lengthy sessions lasting several hours in some cases where the researcher adjusted the parameters of stimulation until the optimum effect was achieved.

The costs involved in the admission to the Western General Hospital for the implantation of the thalamic DBS and the subsequent costs incurred at the rehabilitation hospital (which was dependent on the length of stay) were calculated from costs provided by the local trust providers.

The cost for the number of visits made to the hospital by the researcher was calculated from the rate quoted for a visit by a senior physiotherapist in the Personal Social Services Research Unit unit costs (Netten and Dennett 1996).

5.7.1 (iii) The costs involved in follow-up

The patients were required to attend for review at one, three, six and twelve months post-operatively. The follow-up assessments took place at the Astley Ainslie Hospital where the patient attended as a day case and stayed on the ward for the day so that the assessments could be carried out in the morning and afternoon. There was an obvious direct cost to the NHS for these follow-up assessments which were calculated. There were also indirect costs to patients and their carers as there was a cost in relation to their time in attending these follow-up out-patient appointments. This cost was hard to measure. None of the patients was still able to drive a car owing to their levels of disability and were therefore unable to transport themselves for these visits. Relatives were therefore encouraged where possible to provide or organize transport. Attention was given to the transport costs to and from the Western General Hospital and Astley Ainslie Hopital because in some cases, for example in patients living in England, transport costs were high. There was a standard scale of charges for ambulance journeys, which was based on area in Scotland and on distance in England. The cost of any transport whether it was by ambulance, private car or taxi was not included in the overall calculation of the cost of thalamic DBS.

Readjustments of the IPG parameters were made, as needed during scheduled study visits or during interim visits either of the patient to the hospital or of the research fellow to the patient's home where distance allowed. Again where it was necessary for the physiotherapist to visit the patient at home the cost of these visits was

calculated from the Personal Social Services Research Unit unit costs (Netten and Dennett 1996).

5.7.2 Comparison of the resource use before and after thalamic DBS

The majority of the patients referred for thalamic DBS were moderately to severely disabled (the mean EDSS was 7, range 4.5 – 8.5) and were mostly wheelchair bound. Many of these patients were receiving assisted living services at home either from relatives or community services to maximise their independence and QOL before being referred for implantation of a thalamic DBS. The informal (unpaid) carers were typically spouses who provided physically demanding care often over a long period of time. Carers experience a substantial burden affecting their physical, mental and social well-being. The cost of this burden is well documented (Holmes et al. 1995) and was not discussed here.

The amount of assistance required by patients for activities of daily living was estimated at the pre-operative assessment and then at the 12 month assessment by completing the self-care section of the Functional Independence Measure. The study aimed to discover whether there was a substantial improvement in functional ability with regard to performing activities of daily living with the target upper limb and whether it resulted in any economic benefits (savings in future care costs) in this cohort of patients.

5.7.2 (i) Justification for the methods used

There is increasing emphasis on clinical and cost-effectiveness in the Health Service, which is faced with rising demands but limited resources. Therefore difficult choices

have to be made about how the NHS should use its resources in the most effective overall way. In order to carry out an economic analysis of a new treatment such as thalamic DBS it was necessary to identify the total cost of the procedure and the resources used.

There is also evidence to suggest that this particular group of patients has substantial annual burden costs on the National Health Service. Several studies have shown that the use of and the need for medical and community support services is primarily a function of the MS individual's level of disability (Kraft et al. 1986) (Cervera-Deval et al. 1994). The study mentioned above by Holmes *et al* (Holmes et al. 1995) which investigated the cost of multiple sclerosis reinforced this finding by showing that annual NHS costs depended on the patient's level of mobility and that there was a considerable escalation in NHS costs in patients who are wheelchair-bound. These costs were principally associated with hospital in-patient and out-patient visits, and other treatments not related to general practitioners. Furthermore when considering the social handicaps of patients with MS it was evident that MS patients with cerebellar disorders had significantly more problems with transportation. This finding was relevant to our study, as there was a requirement for the patients to attend the hospital on four occasions during the twelve months after the thalamic DBS was implanted and transport to and from the hospital presented as a problem in many cases.

The overall aim of this study was to evaluate the effectiveness of thalamic DBS and its broader impact on patients and their families. However it was also important to establish the overall cost of the intervention as this has not been addressed in

previous studies. Thalamic DBS has high initial costs but in addition the intervention entails further, perhaps unforeseen costs, which are related to a long-term commitment to maintaining and replacing the pulse generator. However if it were possible to demonstrate that as a result of thalamic DBS there would be a reduction in the use of resources in the longer term then the cost of the intervention might be offset. It was therefore an aim of the study to establish the cost of this intervention and resources used.

CHAPTER 6

RESULTS

6.1 Pre-Operative Presenting Characteristics of Patients with MS

6.1.1 Assessment of suitability for thalamic DBS

6.1.1 (i) Demographic characteristics

During the 4 year study period 37 patients with movement disorders due to multiple sclerosis were referred for assessment of suitability for thalamic DBS. Of the 37 patients referred, 23 (62%) were female and 14 (38%) were male. 34 (92%) patients were right handed and 3 (8%) were left handed. The mean age at the onset of the disease was 29 years. The characteristics of these patients are shown in the table below. The data relating to subject characteristics were found to approximate a normal distribution: therefore, mean data are reported.

Table 6-1: Mean age, duration of MS and of MDMS in patients referred to the study (N=37)

	Minimum	Maximum	Mean	S.D.
Age (years)	25	54	40.1	7.9
Duration of MS (years)	3	20	11.1	5.1
Duration of MD (years)	1	13	4.8	3.2

There was variation with regard to the part of the body affected by the movement disorder within the 37 patients referred to the study. The most common presentation in 30 (81%) of the patients was for the movement disorder to involve the upper limbs, head and trunk. In six (16%) patients the movement disorder affected the upper limbs only (unilateral in four (11%) patients and bilateral in two (5%) patients) and in one (3%) patient the movement disorder predominately affected the axial muscles of the trunk and head.

The upper limbs were therefore affected by a movement disorder in 36 (97%) patients (unilateral in seven (19%)), the head in 31 (84%) patients and the trunk in 28 (75%) patients.

Fifteen patients underwent surgery and 22 patients were deemed not suitable for thalamic DBS for the following reasons: predominant axial tremor (N=6); severe associated neurological dysfunction (N=5); minimal associated disability (N=2); refused operation (N=7); referred for detailed assessment only (N=2).

6.1.2 Patients who underwent surgery

Of the 15 patients who underwent surgery there were seven females (47%) and eight males (53%). Fourteen patients (93%) were right handed and one patient (7%) was left handed. The characteristics of those patients who underwent surgery are shown in Table 6-2. The mean duration of MS was 13 years (range 6-30 years, SD 6.55). The mean duration of time from diagnosis of MS to onset of the movement disorder was 8 years although this ranged from only 1 year to 22 years. The mean duration of

the movement disorder was 6 years and again this ranged from as little as 2 years to 12 years. The patients were moderately to severely disabled (EDSS 4.5 – 8.5) with 8 of the patients being confined to wheelchairs and the other 7 being able to walk only very short distances with the assistance of a walking aid.

Table 6-2: Mean age, duration of MS, details of MDMS and EDSS score of patients who underwent surgery (N=15

	Mean	Median	S.D.	Minimum	Maximum
Age (years)	41.5	42	7.9	27	52
Duration of MS (years)	13.3	12	6.6	6	30
Duration from diagnosis to onset of MD (years)	7.8	7	6.1	1	22
Duration of MD (years)	5.5	5	2.8	2	12
EDSS score	6.9	7	1	4.5	8.5

6.1.2 (ii) Clinical subtype

Of the 15 patients who underwent thalamic DBS and were followed up over the course of the study 10 patients (66%) had entered the secondary progressive phase of MS having initially been diagnosed with relapsing-remitting disease. Five patients (33%) developed cerebellar signs early on in the course of the disease and had what appeared to be a more aggressive form of MS which could probably be classified as progressive-relapsing MS. The disease course was progressive from onset in these patients, with clear acute relapses but periods between relapses were characterized by continuing progression.

6.1.2 (iii) Other neurological symptoms

A neurological examination was carried out at the pre-operative assessment by a neurologist. The Kurtze Functional systems were then scored to provide a baseline assessment of the neurological deficits present in each patient. All 15 patients showed pyramidal and cerebellar dysfunction and the brainstem, sensory and visual systems were affected in the majority of the patients. Only 40 % of patients showed some form of cognitive deficit when assessed with the scale for mental functioning included in the Kurtzke FS.

Table 6-3: Kurtzke FS showing the neurological dysfunction present in patients who underwent surgery (N=15)

Kurtzke's FS	N=
Pyramidal dysfunction	15 (100%)
Cerebellar dysfunction	15 (100%)
Brain stem dysfunction	13 (87%)
Sensory dysfunction	13 (87%)
Visual dysfunction	13 (87%)
Bladder and bowel dysfunction	11 (73%)
Cerebral dysfunction	6 (40%)
Other neurological dysfunction	0

6.2 Results of Surgical Procedures

6.2.1 Surgical treatment of patients

Fifteen patients underwent exploration of the thalamus between October 1996 and February 2000. Four patients had exploration of the right side of the thalamus for a movement disorder of the left arm and 11 patients had exploration of the left thalamus for a movement disorder of the right arm. The dominant arm was the target arm in 11 patients.

The DBS system (DBS electrode and IPG) was implanted in 10 patients. The mean number of passes of the DBS electrode ranged from 1 – 11 (mean 4.9, median 5). In three patients it was not possible for the surgeon to locate a target during the operation to permit an electrode to be implanted to suppress tremor and therefore these patients did not proceed to implantation of any of the DBS equipment and were regarded as unsuccessful attempts. Two of the 12 patients implanted sustained a microthalamotomy effect as a result of the exploration of the thalamus and consequently did not require implantation of the pulse generator

6.2.2 Co-ordinates for the thalamic target

The type of operation performed, the side of the thalamus targeted, the target co-ordinates of DBS electrode implantation and the number of passes of the DBS electrode during the operation are listed in table 6-4.

Table 6-4: Surgical procedure and the thalamic target co-ordinates

Patient (operation)	Side of thalamus	Final target co-ordinates and target points tried in patients in whom a target could not be found	Number of passes
1 (♣)	left	(11, 9, 0)	5
2 (♣)	left	(12, 12, 2)	4
3 (♣)	left	(12, 10, 3)	5
4 (♣)	left	(16, 9, 3)	6
5 (♣)	left	(13, 12, 1)	3
6 (♣)	left	(16, 10, 3)	4
7 (♦)	left	(14, 14, 4)	3
8 (♣)	left	(15, 9, 2)	3
9 (♣)	left	(12.5, 9, 2)	3
10 (♣)	right	(14, 13, 0)	5
11 (♦)	right	(13, 13, 0)	1
12 (♣)	right	(14, 14, 5)	5
13 (#)	right	13,0 13,3 13,-1 14,+2 15,-1 13,+1 17,-3 17,+2	8
14 (#)	left	11,-4 12,-2 13,-1 13,-5 14,-4 15,0 12,2	7
15 (#)	left	13,-2 15,-4 17,-2 19, -2 20, -5 18, 0 18, 4 23. -3 23, 0 23, 3 24, -5	11

Legend for table 6-4:

♣ = Patients who had the DBS system implanted (DBS electrode and IPG)

♦ = Patients in whom a DBS electrode only was implanted

= Patients in whom a thalamic target could not be located to implant an electrode to suppress tremor, therefore no DBS equipment was implanted

Final target co-ordinates (x, y, z) where:

x = distance lateral to AC – PC line (mm)

y = distance from the PC along the AC – PC line

z = distance below the AC – PC line

AC = the anterior commisure, PC = the posterior commissure and AC – PC line = a line connecting the anterior and posterior commissures.

6.2.3 Adverse effects of the procedure

Three patients sustained small thalamo-capsular haematomas (patients 7, 8 and 15). Patients 7 and 8 both had 3 passes of the DBS electrode and patient 15 had 11. They all became symptomatic only after the procedure (patient 7 one hour after and patients 7 and 8 twenty four hours after). Two of the three patients who sustained haematomas (patient 7 and 8) were left with minor residual motor deficits in the upper limb, lower limb and hand at 12 months (see section 6.6.2 (i)). In addition one of these patients (patient 7) had sensory inattention on the hemiparetic side and poorer short term memory than before the operation and the other (patient 8) had transient dysphasia with recovery. Both patients however, had better function in the target limb due to reduction in severity of tremor than pre-operatively. One patient sustained a hypoxic episode (case 6) during scalp closure as a result of hypnoea after propofol dosage. This patient recovered well and was no worse post-operatively on the neuropsychological tests than pre-operatively. The two patients with transient limb weakness (cases 4 and 15) recovered fully to pre-operative levels of general functional status after rehabilitation (as assessed on the Barthel Index).

One patient had a grand mal seizure one week after the IPG was implanted and another 8 weeks after implant. Neither patient had seizures pre-operatively. At the time of the seizures, the stimulation voltages were 3.3V and 3.8V respectively.

One patient developed a staphlococcus aureus infection in the IPG site in the pectoral region one month after the IPG was implanted. Aspiration of the collection and antibiotic therapy (oral and intra-venous) was given and the infection seen to resolve. However due to reactivation of the infection the IPG and extension lead were removed 11 months after operation. The DBS electrode was left *in situ.*

6.2.4 Record of follow-up assessments

Eight of the 10 patients (1, 2, 3, 4, 5, 6, 9 and 10) who had thalamic DBS systems implanted (♣) were compared pre-operatively and 12 months after operation with the DBS off and only 7 of the same 10 patients (1, 2, 3, 5, 6, 9 and 10) were compared pre-operatively and 12 months after operation with the DBS on as patient 4 had the IPG removed one month before the final assessment. Twelve month data was not available for patients 8 and 12. Patient 12 had implantation of a thalamic DBS in February 2000 and consequently one month data only could be obtained due to the time limit of the study. Patient 8 did not attend for the 12 month follow up assessment despite several dates being arranged. The researcher had problems contacting the patient in order to try to arrange for her to be visited at home which was not straight forward because of geographical inaccessibility.

There were also problems with collection of data in the two patients (7 and 11) who had thalamic DBS electrodes implanted only (♦). Patient 11 could not be assessed because of the time limit of the study. Patient 7 lived in Sheffield and after operation required rehabilitation which was organised locally in Sheffield. The researcher travelled to Sheffied to carry out the one month post-operative assessment. However

when the 12 month post-operative assessment was due to be performed the patient's parents refused assessment.

Follow-up assessments using the MFTRS and the JTHF were performed on the three patients in whom no equipment was implanted (#). The data is presented in the graphs shown in the individual patient case studies (section 6.5).

Table 6-5: Record of follow-up assessments

	Time of Assessment									
Patient	**Pre-op**	**1 month**		**3 months**		**6 months**		**12 months**		
DBS on/off		**on**	**off**	**on**	**off**	**on**	**off**	**on**	**off**	**Reasons for missing data**
1 ♣	*	*	*	*	*	*	*	*	*	
2 ♣	*	*	*	*	*	*	*	*	*	
3 ♣	*	X	X	X	X	*	*	*	*	DNA
4 ♣	*	*	*	*	*	*	*	-	*	IPG removed at 11 m
5 ♣	*	*	*	*	*	*	*	*	*	
6 ♣	*	*	*	*	*	*	*	*	*	
7 (♦)	*	-	*	-	-	-	-	-	X	geographical inaccessibility
8 ♣	*	*	*	*	*	*	*	X	X	DNA –social problems Geographical inaccessibility
9 ♣	*	*	*	*	*	*	*	*	*	
10 ♣	*	*	*	*	*	*	*	*	*	
11 (♦)	*	-	*	-	X	-	X	-	X	Time limit of study
12 ♣	*	*	*	X	X	X	X	X	X	Time limit of study
13 (#)	*	-	*	-	*	-	*	-	*	No DBS to assess
14 (#)	*	-	*	-	*	-	*	-	*	No DBS to assess
15 (#)	*	-	*	-	*	-	*	-	*	No DBS to assess

♣ = DBS system implanted (DBS electrode and IPG)

♦ = DBS electrode implanted

= Unsuccessful attempts

DNA = did not attend, * = Assessment completed, X = missing data, - = no assessment required

6.3 Results of stimulation

6.3.1 Parameters for stimulation with the IPG

Patients required their own unique parameters for stimulation to suppress tremor. Reprogramming of the stimulator was often required especially if the patient had experienced a microthalamotomy effect which tended to wane in the first months after surgery. Some patients required many visits to achieve optimum tremor suppression as time progressed whereas others only needed a few: the mean number of visits for reprogramming was 5, range 2 – 14. The mean amplitude, frequency and pulse width on discharge from hospital and at 12 months were 2.7V, 120Hz, 120μs and 3V, 160Hz, 110μs respectively. The most common arrangement of electrode polarity was to assign a positive polarity to the IPG casing and to have a negative contact at the tip of the DBS electrode in the thalamus.

Parameters for stimulation (amplitude, frequency, pulse duration) and the electrode arrangement on discharge from hospital and at 12 months are shown in Table 6-6.

Table 6-6: Stimulation details

Patient	DBS parameters on D/C				Final DBS parameters			
	Amp (V)	Freq (Hz)	Pulse dur. (μs)	Electrode polarity	Amp (V)	Freq (Hz)	Pulse dur. (μs)	Electrode polarity
1	1.6	135	60	3+ 2–	2.2	135	90	Case+ 2–
2	2.9	145	60	2+ 0–	3.5	185	120	Case+ 1–
3	3.3	70	160	Case+ 3–	2.8	130	90	Case+ 3–
4	3.3	30	120	3+ 0–	2.5	135	60	3+0–
5	3.3	30	150	2+ 0–	3	170	120	Case+ 0–
6	3.3	145	90	3+ 1–	3.5	170	90	3+ 1–
7	2.2	185	120	Case+ oth–	2.2	185	120	Case+ oth–
8	2.9	135	150	Case+ oth–	5	135	150	Case+ oth–
9	2.2	135	150	Case+ 0–	3.9	160	150	Case+ 0–
10	1.8	130	120	Case+1-	*	*	*	*
Mean	2.7	114	118		3	153	110	
Median	2.9	135	120		2.9	148	120	

Legend for table 6-6: amp = amplitude measured in Volts, freq = frequency measured in pulses/sec (Hertz), p.width = pulse width/duration measured in micro seconds (μs), electrodes = polarity of electrical contacts on the tip of the electrode (numbered 0, 1, 2, 3 where 0 is the deepest in the thalamus). Case = the IPG casing which can either be positive or off, oth = all other electrodes. * = Parameters for stimulation unchanged from those at discharge as operation performed in February 2000.

6.3.2 Adverse effects of thalamic DBS

There were no intractable complications related to thalamic DBS. Problems due to the thalamic stimulation were typically mild and were generally reversible or easily controlled when the parameters of stimulation were changed or stimulation was discontinued. Some patients reported transient paraesthesiae when they first turned the DBS device on each day. Typically the paraesthesiae involved the target side of the body and mostly affected the target upper limb. The abnormal sensation usually abated within several seconds after turning the device on. In two patients unwanted side effects in the form of dysphasia and diplopia persisted when certain electrode arrangements were tried and the DBS was switched on. IPG parameters were therefore adjusted to eliminate or reduce these unwanted side effects.

6.3.3 Patient's ability to turn the DBS on and off

Turning the thalamic DBS on and off was not straight forward and only three of the 10 patients who had DBS implanted were able to do this independently using the hand-held magnet. The other seven relied on others to do it for them.

All patients were issued with a transistor radio to enable them to check whether or not the stimulator had been turned on or off successfully with the magnet. The patient was instructed to turn the radio on and tune it to 530 kHz on the AM waveband. The patient then held the radio over the stimulator (IPG) and if it was switched on an interference sound was emitted from the radio. If the stimulator (IPG) was off only the faint hissing noise from the radio could be heard.

6.4 The Effect of Thalamic DBS

The hypothesis that the severity of tremor amplitude would decrease and performance of upper limb function would improve after implantation of thalamic DBS was proposed (Chapter 1 – section 1.7)

The MFTRS was used to investigate change in severity of tremor and the JTHF was used to measure functional performance of the upper limb. Comparisons were made between scores of severity of tremor and the number of successful Jebsen subtests at the pre-operative and later assessments (1month, 3 months, 6 months and 12 months) and form the basis of the following findings.

The mean and median scores for the rating of severity of tremor and successful number of Jebsen subtests scored were compared and there was little difference between them (Appendix 37 and 38). As the majority of data is at the ordinal level of measurement, non parametric statistical presentation of the results was most appropriate. Further it was argued in Chapter 2 that items on such scales are most appropriately viewed as a profile of the individuals severity of tremor (in the case of the MFTRS) and ability to perform ADL (in the case of the FIM and Barthel Index). However, in order to use these measures to look at change in outcome during the 12 months of the study, a pragmatic approach was taken and therefore for some analysis the data was summated. Data was collected at pre-operatively and at 1 month, 3 months, 6 months and 12 months after operation. At each of the post-operative evaluations the researcher carried out two assessments: one with the DBS on and one with the DBS off.

6.4.1 The effect of thalamic DBS on severity of tremor over time

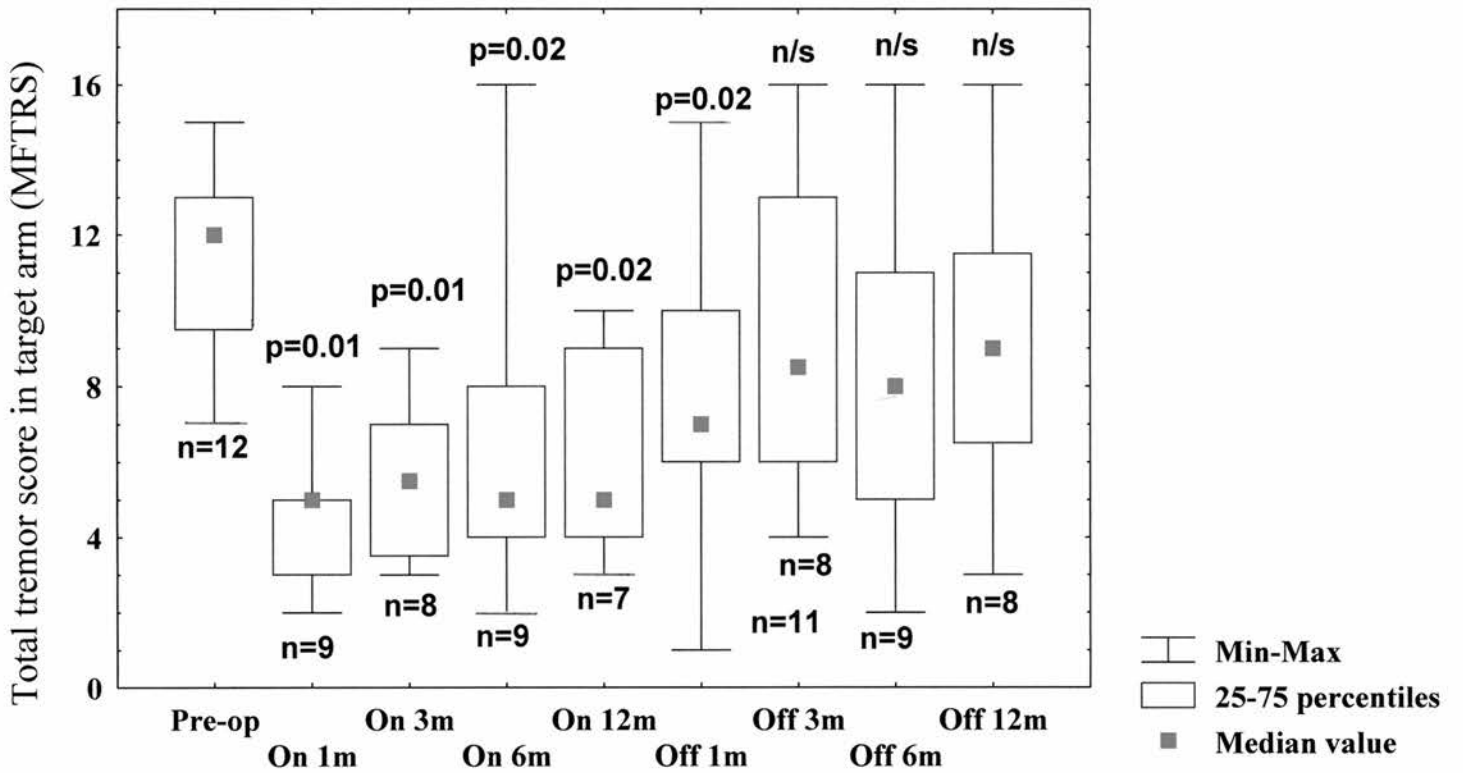
6.4.1 (i) Comparison between the total tremor rating scores with the DBS on and off at pre-operative and post-operative assessments

The components of tremor (postural a), postural b), kinetic/intention and goal-related) were scored on a 5 point scale (0 – 4), with a higher score indicating increased severity of tremor. The scores for the different components were summed to give a total tremor score for the target arm (the best possible score = 0, the worst possible score = 16).

Figure 6-1 illustrates the median scores, inter-quartile ranges and extreme values for the total tremor scores of the target arm at the pre-operative and later assessments with the DBS on and off. Pre-operative tremor rating scores ranged from 7 – 15. After operation with the DBS on the scores ranged mainly from 1 – 10 although there was an outlying score of 16 at the 6 month assessment. After operation with the DBS off the worst possible tremor rating score of 16 was present at the 3, 6 and 12 month assessments. Tremor severity scores were lower at the 1 month post-op assessment with the DBS off (scores ranged from 1 – 15) due to the beneficial influence of a microthalamotomy effect in some patients in the first month after implantation. The median total tremor scores when the DBS was on were either 5 or 6 and were lower than when the DBS was 'off' when the median scores range from 7 to 9. However the median scores when the DBS was off were all lower than the pre-operative median score indicating that there was a reduction in severity of tremor scores even without any stimulation which was still evident 12 months after the operation.

Wilcoxon matched pair tests were used to compare conditions and involved only the patients tested on both occasions. Tabulated data included all patients tested on one or both occasions. P values were given without adjustment for the number of comparisons made as this was an exploratory/pilot study and common adjustments such as the Bonferroni procedure were considered too conservative in this context. The severity of tremor when the DBS was on at each of the 4 post-operative assessments was significantly reduced compared with pre-operatively. It was also significantly reduced when the DBS was off at the 1 month assessment, perhaps as a result of a microthalamotomy effect.

Figure 6-1: Comparison of the total tremor scores for the target arm at pre-operative and later assessments (1,3,6 and 12m) with the DBS on and off



P<0.05, lower total tremor score with DBS than the preimplant rating

n/s = not significant

6.4.1 (ii) Comparison of the total severity of tremor with the DBS on and off at post-operative evaluations

At each of the post-operative evaluations two assessments were carried out by the researcher: one with the DBS off and one with the DBS on. The assessments were performed in a random order and the researcher was blind to the nature of the assessment. The results of the 2 assessments at each post-operative evaluation were compared : there was a significant reduction in severity of tremor between the mean total tremor rating scores for the target arm when the DBS was on compared to when it was off at all the post-operative assessment intervals (1, 3, 6 and 12 months).

Table 6-7: Significance levels concerning total tremor scores in the target arm with the thalamic DBS on versus off at each post-operative evaluation

	1 month (N=8)	3 months (N=8)	6 months (N=9)	12 months (N=7)
Total tremor score with DBS ON versus OFF	**0.02***	**0.01***	**0.03***	**0.04***

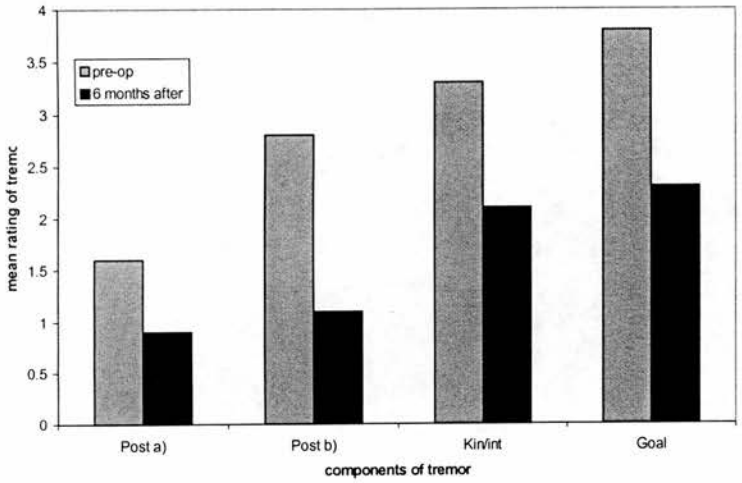
* = $p<0.05$. Wilcoxon matched pairs tests were used to compare on with off.

6.4.1 (iii) Comparison of the different types of tremor between pre-operative and 6 month evaluations

The mean scores for the different types of tremor in 9 patients assessed pre-operatively and at 6 months after implantation of a thalamic DBS (patients 1, 2, 3, 4, 5, 6, 8, 9, and 10) with the DBS on were compared. The mean scores of goal-related tremor severity were higher than all other components of tremor at both the pre-operative and the 6 month post-operative evaluations; some change was apparent in

all components of tremor, especially in the severity of postural b) tremor at 6 months, compared with pre-operative scores.

Figure 6-2: Mean ratings of the different types of tremor at pre-operative and 6 month assessments with the DBS on



Legend:

Post a) = postural a) tremor

Post b) = postural b) tremor

Kin/int = kinetic/intention tremor

Goal = goal- related tremor

6.4.1 (iv) Comparison of the different types of tremor in individual patients

The different types of tremor in the target arm (postural a), postural b), kinetic/intention and goal-related) were scored on a 5 point scale (0 – 4). The severity of tremor was rated by amplitude and the definitions of the size of the amplitude were: 0 = no tremor; 1 = slight tremor, maximal amplitude <1cm; 2 = mild tremor, amplitude 1 – 5cm; 3 = moderate tremor, amplitude 5 – 10 cm; 4 = severe tremor, amplitude >10cm. A higher score therefore indicated increased severity of tremor.

In all patients ratings of the different types of tremor either stayed the same or improved apart from in one patient (patient 9) whose postural b) tremor worsened by one point on the scale (from 3 to 4) when a comparison of the tremor rating scores was made between the pre-operative and the 6 month post-operative assessments with the DBS on (N=9).

Two patients (patients 2 and 3) had no evidence of postural a) tremor before or after operation. There was no change in the rating of postural a) tremor in 2 patients (patients 4 and 9) at the 6 month post-operative assessment. In the other 5 patients in whom the rating of postural a) tremor ranged from 1 to 3 pre-operatively, postural a) tremor decreased and was absent in 3 patients at the 6 month post-operative assessment.

There was a wide variation in scores of severity of postural b) tremor amongst the nine patients, with all grades of severity of tremor being present pre-operatively (1 – 3). The majority (N = 6) of patients had marked postural b) tremor before operation

and all patients except patient 9 demonstrated an improvement at the 6 month post-operative assessment.

Tremor was most severe pre-operatively for kinetic/intention and goal-related types of tremor. The scores for kinetic/intention tremor and goal related tremor stayed the same (patient 4 scored 3 before and after for kinetic/intention tremor and patients 4 and 6 scored 4 before and after for goal-related tremor) or improved at the 6 month post-operative assessment.

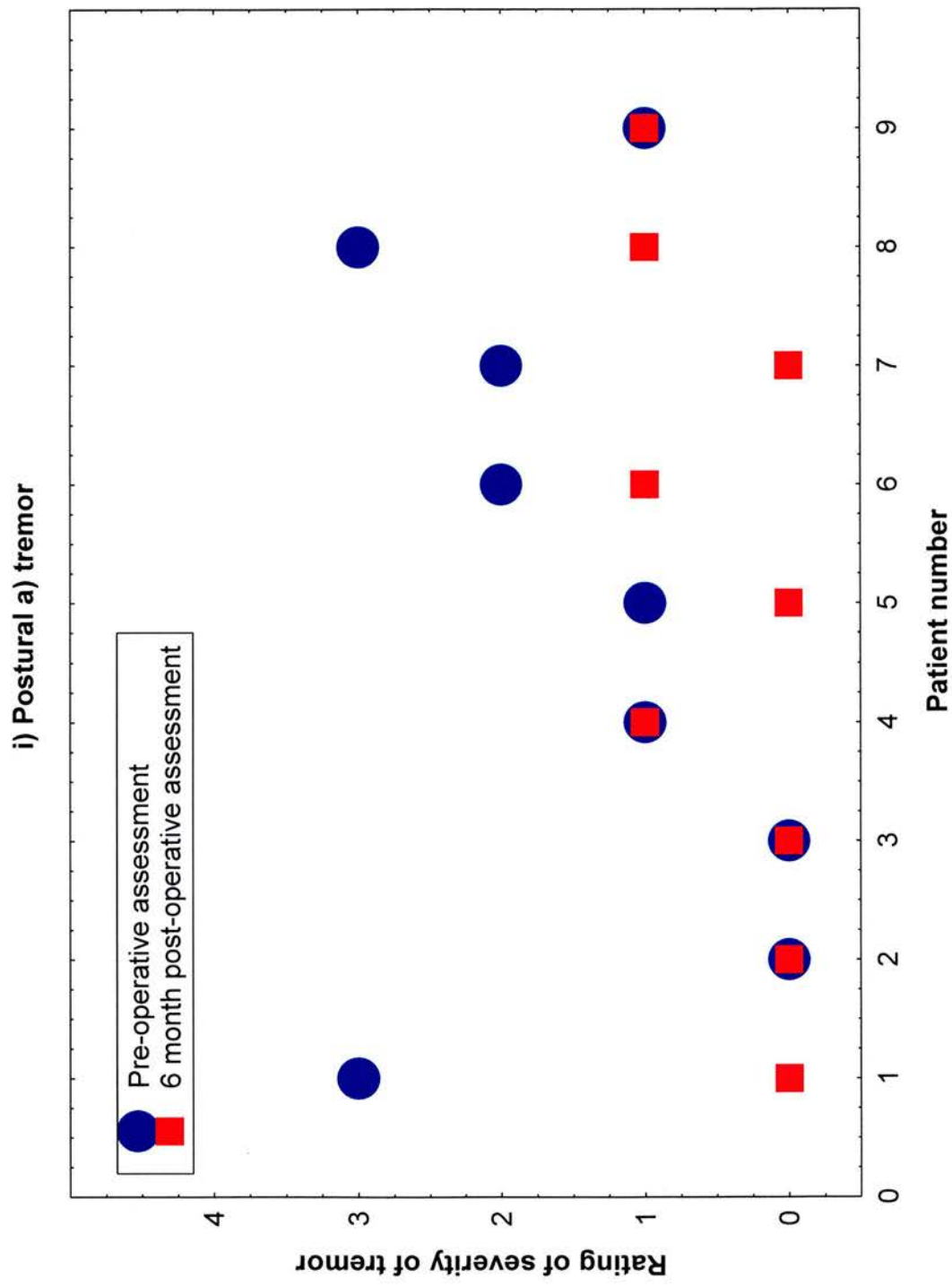
Figure 6-3 (i-iv): Comparison of the tremor rating scores for different types of tremor in the target arm of individual patients at pre-operative and 6 month assessments with the DBS on

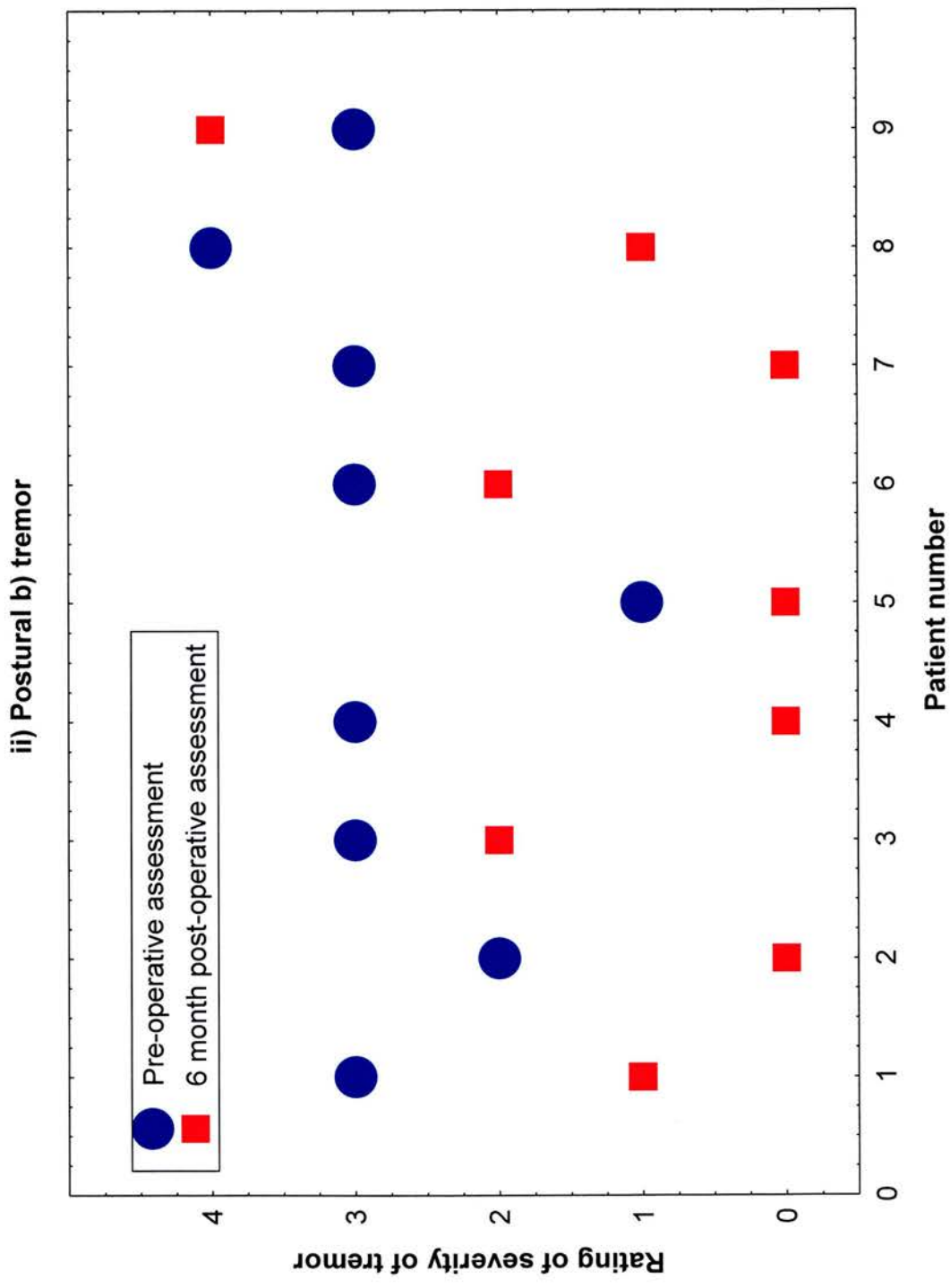
i. postural a) tremor

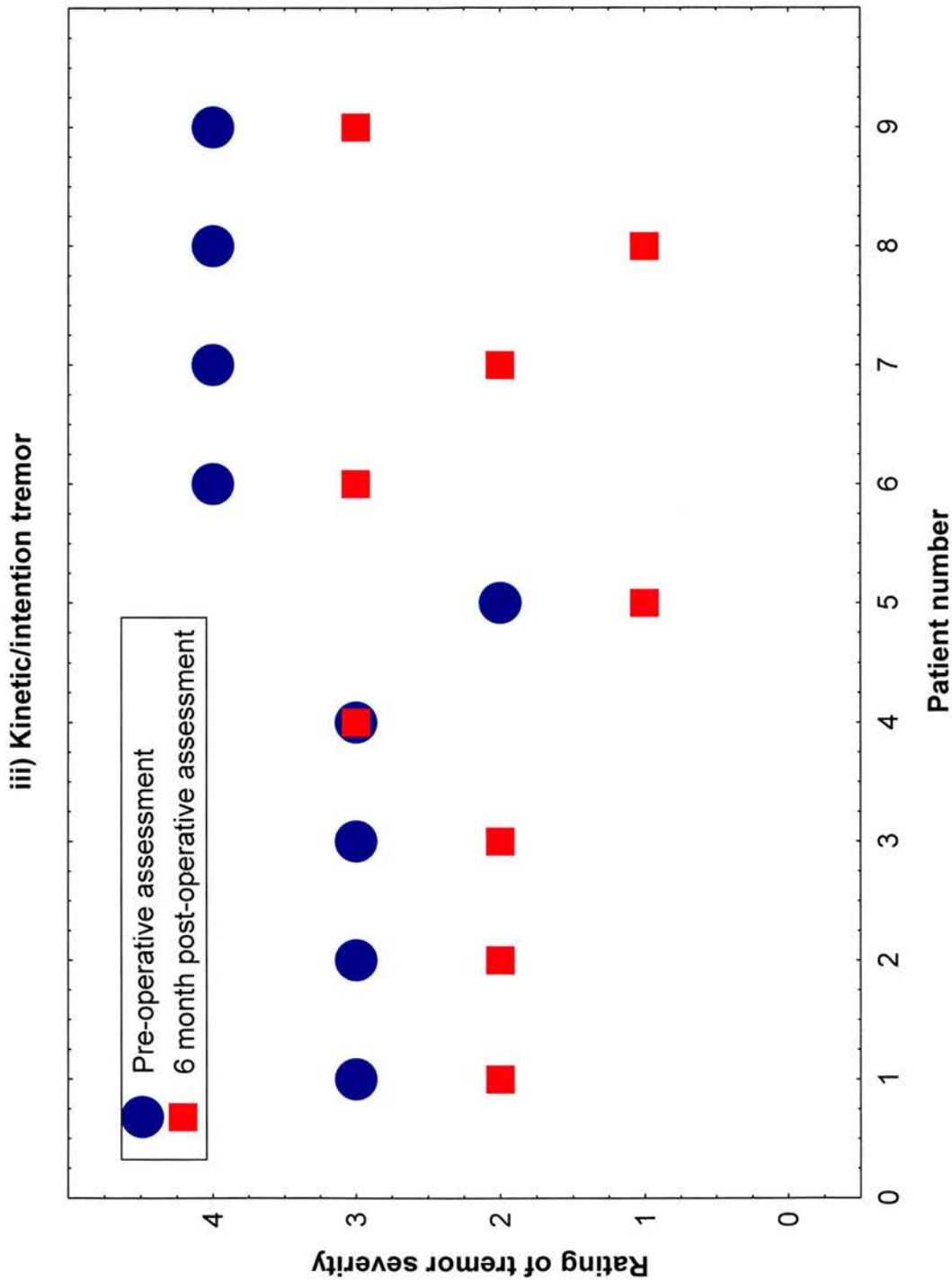
ii. postural b) tremor

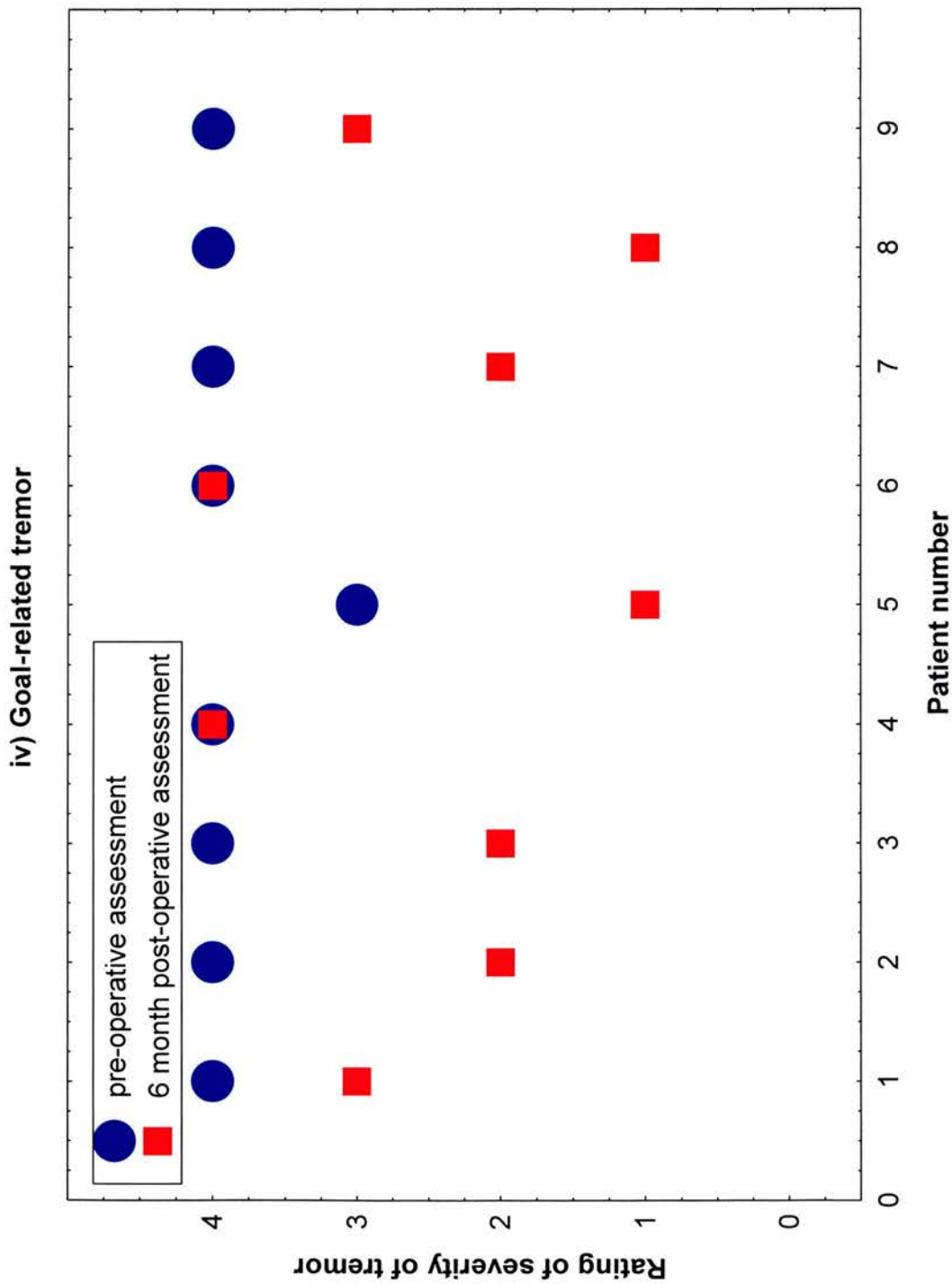
iii. kinetic/intention tremor

iv. goal-related tremor


i) Postural a) tremor
Pre-operative assessment
6 month post-operative assessment
Rating of severity of tremor
0
1
2
3
4
Patient number
0
1
2
3
4
5
6
7
8
9


ii) Postural b) tremor
Pre-operative assessment
6 month post-operative assessment
Rating of severity of tremor
Patient number
0
1
2
3
4
5
6
7
8
9


iii) Kinetic/intention tremor
Pre-operative assessment
6 month post-operative assessment
Rating of tremor severity
0
1
2
3
4
Patient number
0
1
2
3
4
5
6
7
8
9


iv) Goal-related tremor
pre-operative assessment
6 month post-operative assessment
Rating of severity of tremor
0
1
2
3
4
Patient number
0
1
2
3
4
5
6
7
8
9

6.4.2 The effect on the total number of successful Jebsen subtests with the target arm

6.4.2 (i) Comparison of the total number of successful Jebsen subtests with the DBS on and off at the pre-operative and post-operative assessments

The 7 subtests of the Jebsen Test of Hand Function ranged in order of difficulty and meant that even the patients who were most disabled by the movement disorder in the target arm were usually able to perform at least one subtest successfully. Some subtests, which involved turning over cards and lifting heavy cans onto a shelf, were easier to perform than some of the other subtests such as picking up kidney beans with a teaspoon and putting them into a container. The writing task was probably the most difficult subtest both before and after operation. Patients with severe upper limb movement disorders had great difficult trying to grasp the pen and put the pen onto the paper and had even greater difficulty writing. Other factors such as reduced sensation and muscle weakness in the hand and poor eyesight also influenced the performance of the subtest and many patients had not attempted to write for many years.

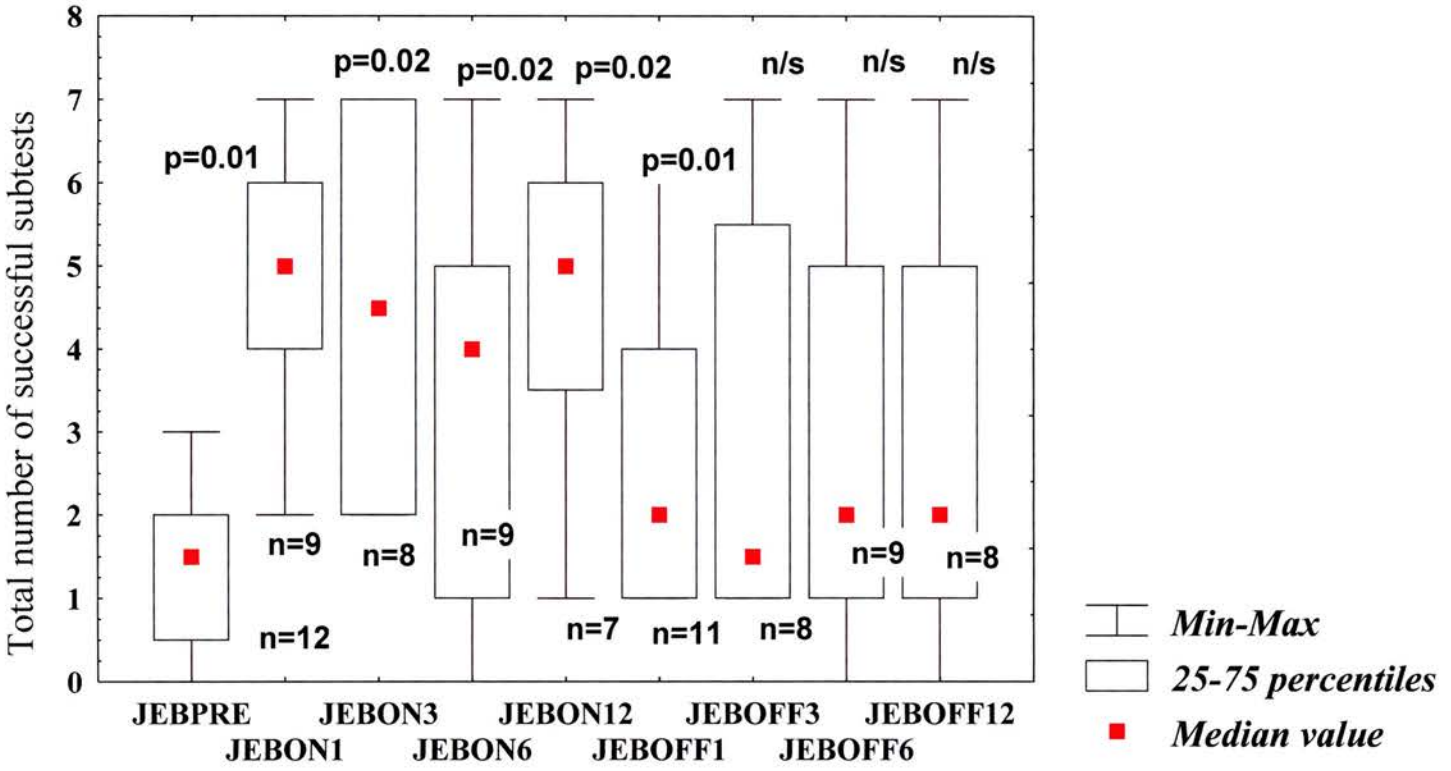
The test was scored by counting the number of successful subtests performed by the patient: allocating 1 for a pass and 0 for a fail. The higher the score the better the performance on the subtests (best possible score = 7, worst possible score = 0).

Figure 6-4 shows the median Jebsen scores, the interquartile range and extreme values for the total number of successful subtests of the Jebsen Test of Hand Function. The median scores when the DBS was on were either 5 or 6 indicating that patients performed more subtests successfully than when the DBS was off where the

median scores were only 1.5 or 2. The median scores when the DBS was off were the same as the median score pre-operatively. The range of scores was small pre-operatively (0 – 3) and was larger at the post-operative assessments, where scores ranged from 0 – 7 regardless of whether the stimulator was on or off.

As shown in Figure 6-4 the total number of Jebsen subtests passed at each of the 4 post-operative assessment was significantly greater when the DBS was on than the total number of Jebsen subtests passed pre-operatively. There was also a significant increase in the number of Jebsen subtests passed when the stimulator was turned off at the one month post-operative assessment compared with the pre-operative assessment. This was attributable to a microthalamotomy effect which subsequently waned. The differences in the number of subtests passed at the other assessment when the DBS was off compared with pre-operative assessment were not significant.

Figure 6-4: Comparison of total number of successful Jebsen subtests with the target arm at preoperative and later assessments (1,3,6,& 12m) with the DBS on and off



p<0.05, greater number of successful subtests with DBS than preimplant

n/s = not significant

6.4.2 (ii) Comparison of the total number of successful Jebsen subtests with the DBS on and off at the post-operative assessments

When a comparison was made between the assessment when the DBS was on compared with the assessment when the DBS was off at the same evaluation, there was a significant difference in the number of Jebsen subtests passed at the 1 month, 3 month and 12 month evaluations showing that the DBS was having an effect. However, there was no difference at the at the 6 months post-operative evaluation.

Table 6-8: Significance levels concerning the total number of successful Jebsen subtests with the DBS on versus off with the target arm at each post-operative assessment.

	1 month (N=8)	3 months (N=8)	6 months (N=9)	12 months (N=7)
Number of successful subtests with the DBS ON versus OFF	**0.02***	**0.02***	**0.07**	**0.04***

* = $p<0.05$. Wilcoxon matched pairs tests were used to compare on with off

6.4.3 Comparison of pre-operative and 6 month post-operative assessments of the non-target arm

Fourteen patients (93%) had some evidence of a movement disorder in the non-target arm. The target arm was assessed in a total of 11 patients (cases 1, 2, 3, 4, 5, 6, 9, 10, 13, 14 and 15) at both the pre-operative and 12 month post-operative assessments. The mean total tremor score for the non-target arm pre-operatively was 8.7 (median score = 8, scores ranged from 0 to 15) and 9.4 (median score = 10, scores ranged from 1 to 14) 12 months after operation. The mean number of Jebsen subtests passed

pre-operatively was 3.3 (median score = 2, scores ranged from 1 to 7) and 2.5 (median score = 2, scores ranged from 0 to 7) 12 months after operation. The mean and median scores suggested some slight deterioration although this change was not significant in the total score for severity of tremor ($p = 0.53$) or the number of Jebsen subtests passed ($p = 0.08$) with the non-target arm at the 12 month post-operative assessment compared with the pre-operative assessment.

6.4.4 The effect on cognitive function

Twelve of the fifteen patients who underwent stimulator implantation completed the brief collection of neuropsychological tests described in Chapter 2, at varying intervals up to 4 weeks before surgery and approximately four weeks after. Two of the patients who had thalamic DBS implanted had no preoperative neuropsychological assessment through oversight (but when assessed post-operatively were typical of other participants). One patient had no post-operative assessment because of geographical inaccessibility but was typical of other participants when assessed pre-operatively. Most patients who did not proceed to stimulator implantation completed the collection of tests once only (as part of their initial assessment). One experienced neuropsychologist (R. Taylor) carried out all the testing.

Most participants showed neuropsychological impairment preoperatively when compared with 54 normal volunteer control participants (22 male, 32 female; mean age = 38.4, SD = 15.2) tested on two occasions on average 6 (SD = 2) weeks apart. In those who proceeded to implantation, the mean initial test score (142, SD = 13)

was far below the level of comparable normal controls (168, SD = 4; n = 54). Only one patient who proceeded to implantation (and one patient who did not) scored at or better than the fifth centile level (score = 159) of normal controls.

On this test collection, normal controls show a small mean test-retest practice effect of +1.4 (SD = 3) points. For patients assessed both before and after surgery, the mean score was 142 (SD = 13) before surgery and 140 (SD = 15) after (Mean change –2, SD = 6; Wilcoxon p = 0.476; paired t-test, p = 0.397). The lack of significant change was not attributable to ceiling or floor effects on the tests used. Two patients showed more decline than the fifth centile level of decline in normal controls (5 points; N = 54). One of these showed a decline of 16 points and the other 7 points, both probably as a result of vascular complication. The one patient who was not tested post-operatively (for geographical reasons) may have shown some decline as a result of a thalamic haematoma which occurred during the operation. All other patients showed little or no change on assessment of mental functioning.

There was no correlation between mental function and severity of tremor in the patients referred to the study with MS (Spearman's $\rho = 0.15$, $p = 0.48$, $N = 24$) or in the group of patients who were selected for operation to implant a thalamic DBS ($\rho = 0.16$, $p = 0.61$, $N = 13$) when tested pre-operatively. The only significant correlation found between neuropsychological performance and illness variables was that poorer mental functioning correlated with longer duration of MS ($\rho = -0.610$, $p = 0.004$, $N = 20$). This was not surprising.

6.5 Individual Case Studies of Patients who Underwent Surgery

The following pages display graphic presentations of individual case studies of the 15 patients who underwent surgery. They show both the microthalamotomy effect if present and the effect of thalamic DBS over time on both the scores for severity of tremor in the target arm and the number of sucessful Jebsen subtests performed with the target arm.

Two figures are shown for each patient (figures a and b). The legends, labelling and titles shown in the figures for patient 1 apply to all the subsequent figures and have been omitted to avoid repetition and aid clarity. The score for severity of tremor is the total tremor score for the different components of tremor in the target arm and is referred to in the text as the 'tremor score'. The score for the performance of upper limb function is the number of subtests of the JTHF passed by the patient with the target arm and is referred to in the text as the 'Jebsen score'.

Figures 6-5 – 6-19: Effect of thalamic DBS (and microthalamotomy) over time on total tremor scores and the number of Jebsen subtests performed successfully with the target arm

Figure a

Figure a shows the changes in total tremor rating score (MFTRS) for the target arm over time. Data are shown for pre-operative (baseline) assessment and for one, three, six and twelve month follow-up with the DBS on and off.

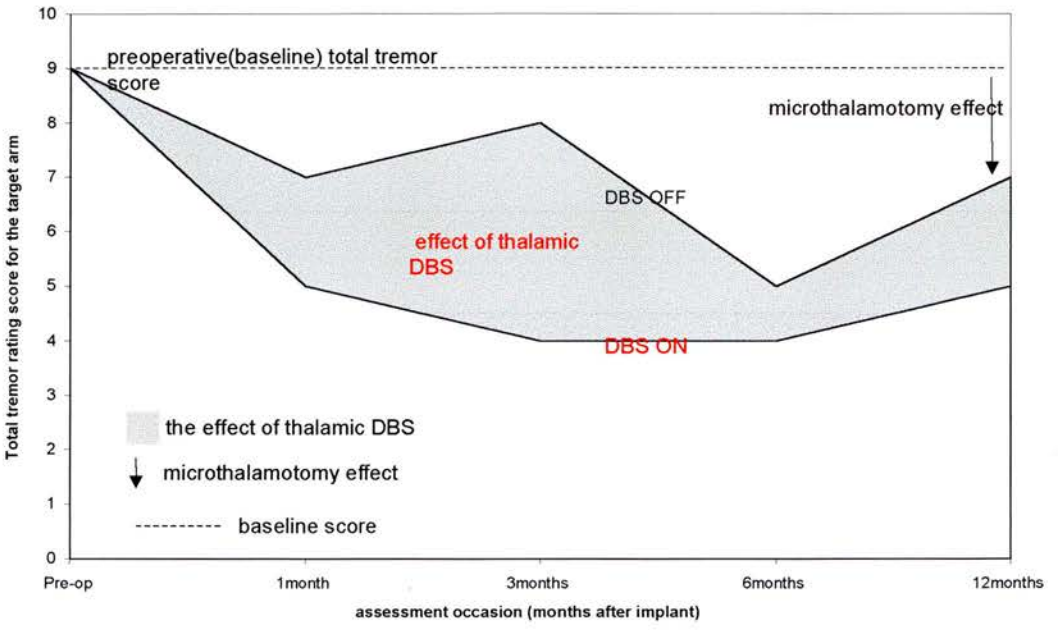
Figure b

Figure b shows the total number of successful Jebsen subtests with the target arm over time. Data are shown for pre-operative (baseline) assessment and at one, three, six and twelve month follow-up assessments with the DBS on and on.

Figures 6-5: Patient 1

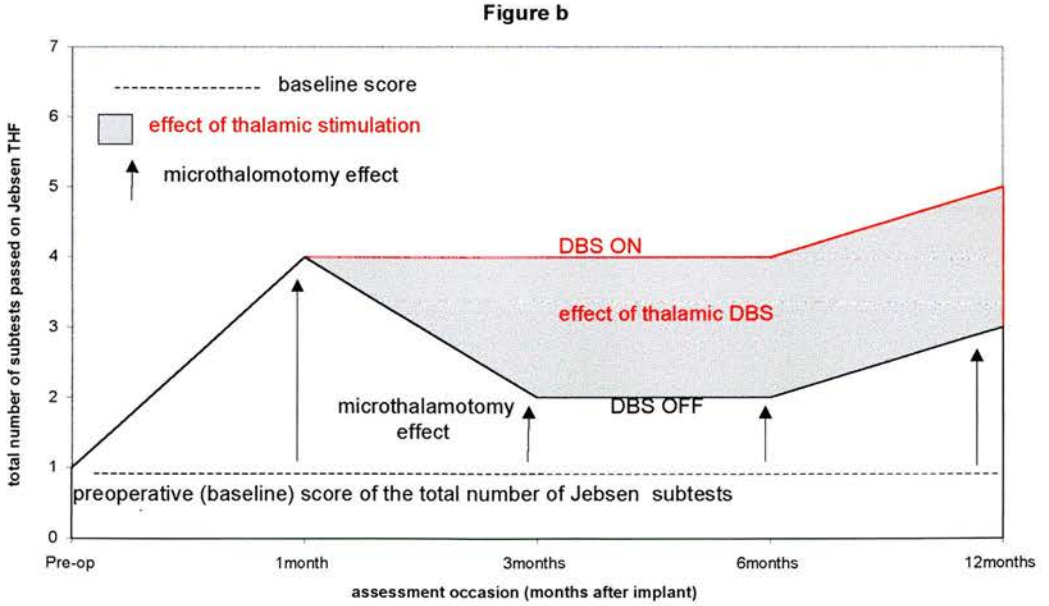
A 36 year old man with MS for 10 years with a movement disorder affecting the dominant right arm which had been present for 5 years.

Figure a



The figures show that the patient has experienced a persisting microthalamotomy effect since the operation. The patient shows some improvement in tremor scores and Jebsen scores as a result of DBS and a microthalmotomy effect at the 12 month post-operative assessment.

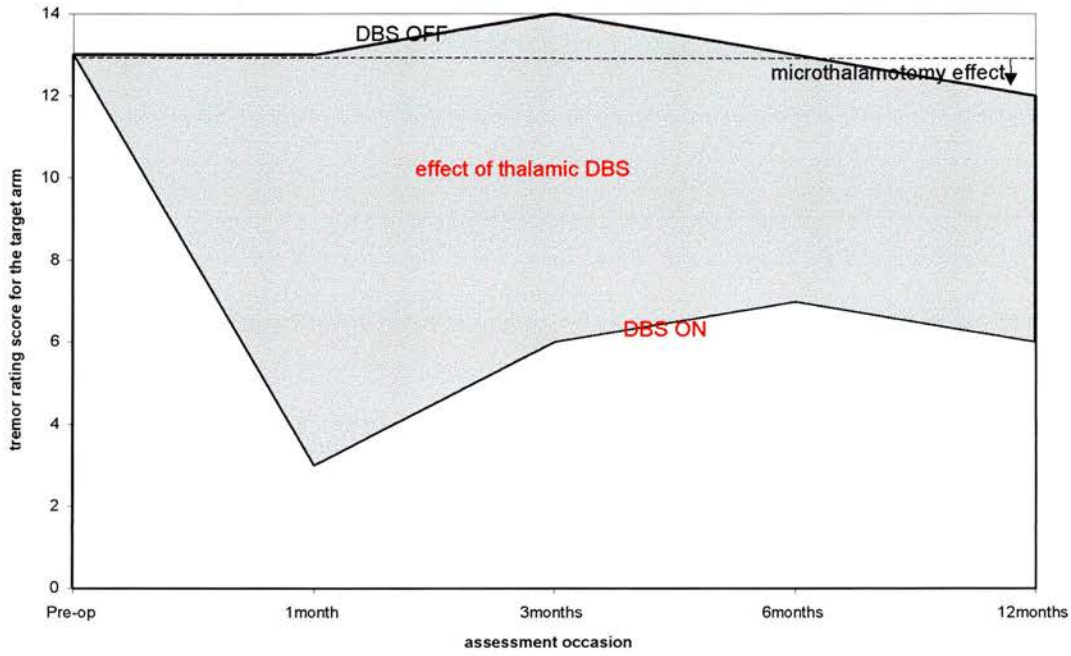
Figure b



Figures 6-6: Patient 2

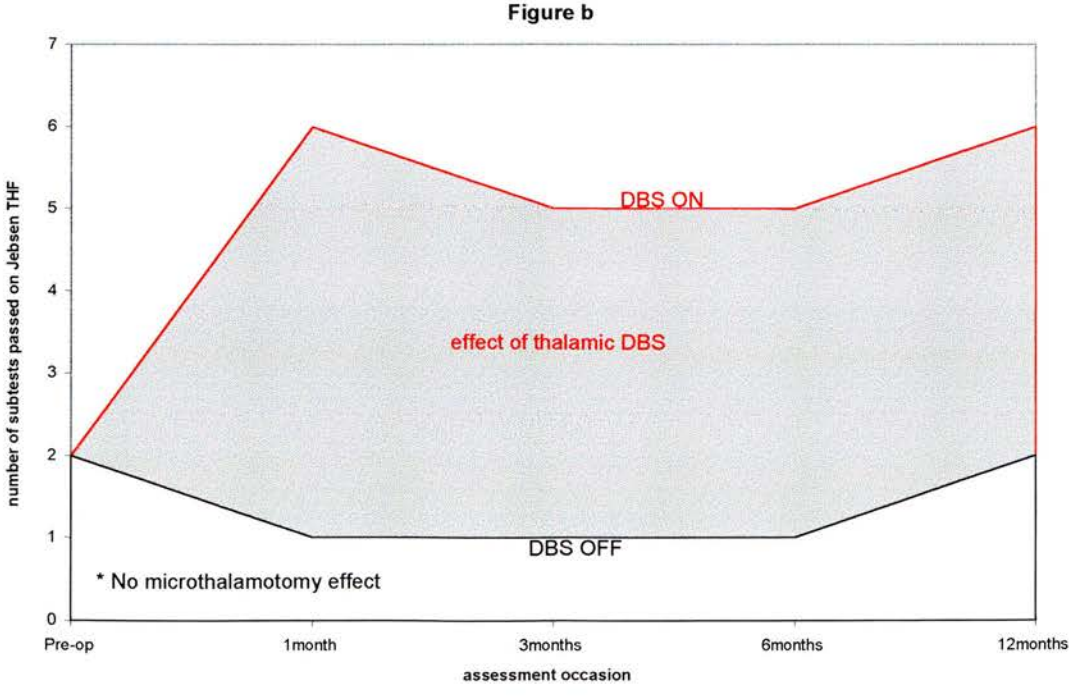
A 52 year old man with MS for 20 years with a movement disorder affecting the dominant right arm which had been present for 12 years.

Figure a



The figures show that there was no microthalamotomy effect after implantation. There is considerable benefit in both the reduction in the severity of tremor and improved successful performance of the Jebsen subtests 12 months after operation.

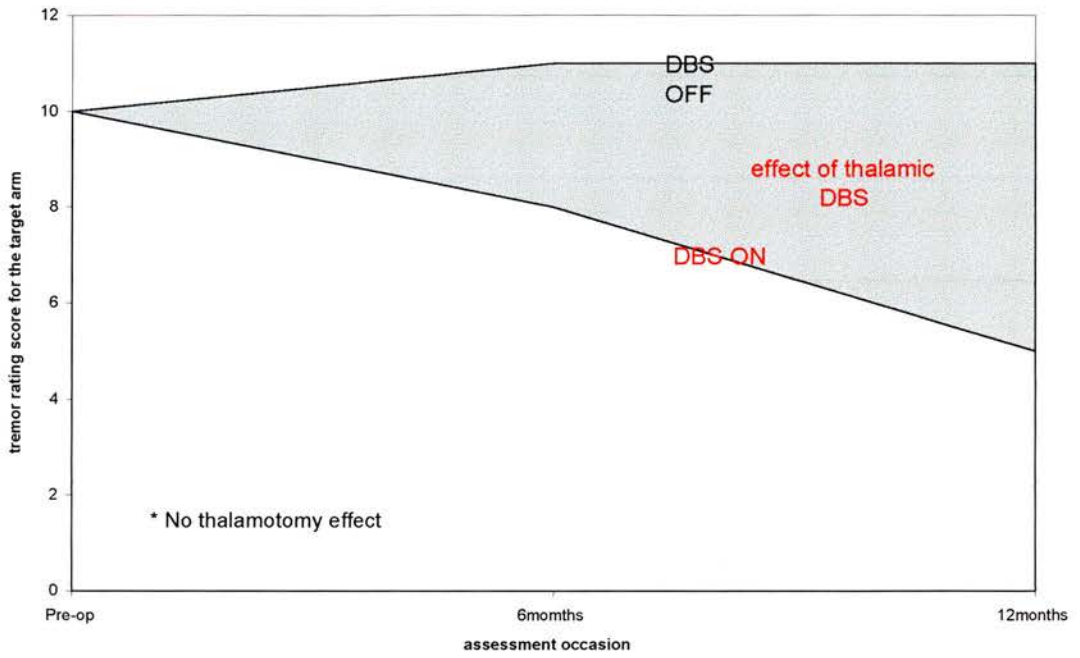
Figure b



Figures 6-7: Patient 3

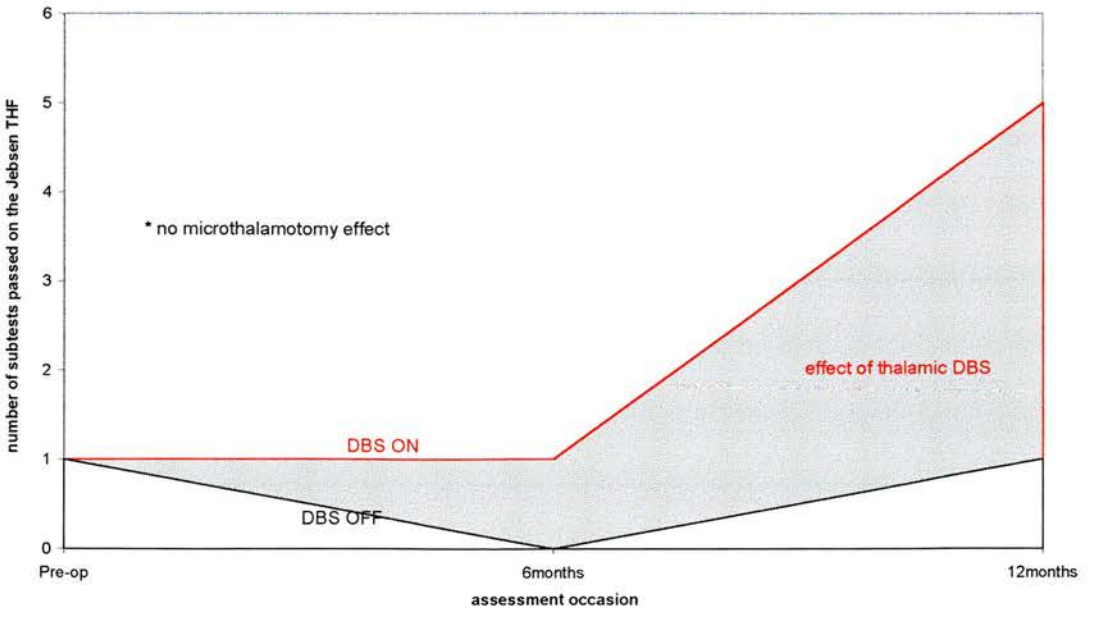
A 33 year old woman with MS for 6 years and a movement disorder affecting both of the upper limbs, the head and trunk. The target arm was her dominant right arm.

Figure a



No microthalamotomy effect was present after the operation. The patient demonstrated a reduction in the severity of tremor and improved performance on the Jebsen subtests at the 12 month assessment.

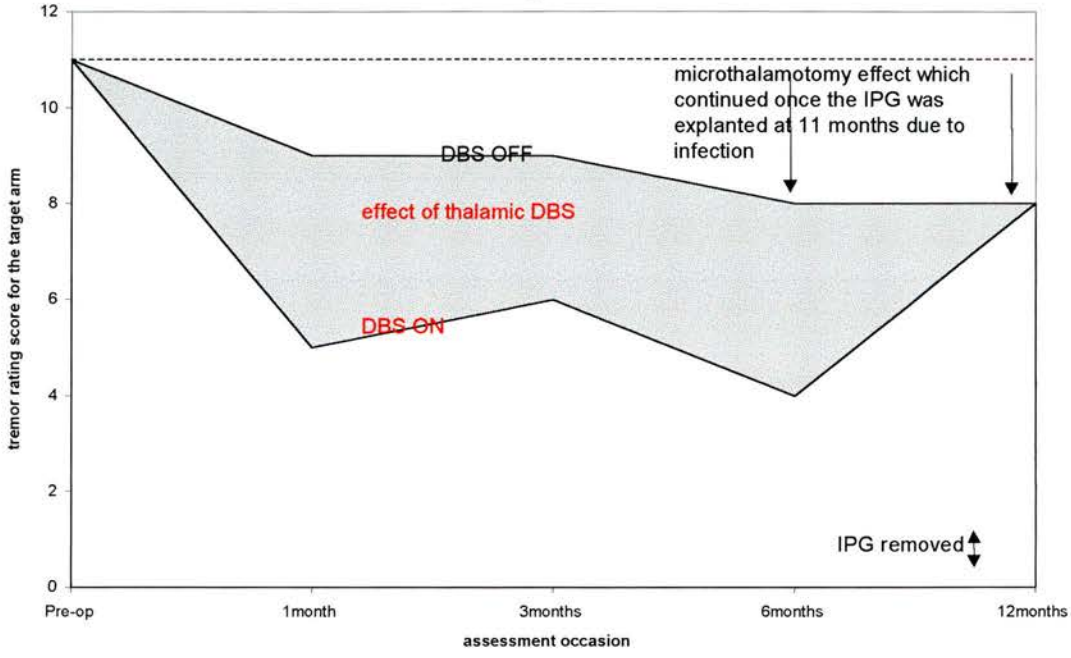
Figure b



Figures 6-8: Patient 4

A 46 year old woman with MS for 8 years with a movement disorder affecting both of the upper limbs, the head and the trunk. The target arm was the dominant right arm.

Figure a



The figures show that the patient benefited from a microthalamotomy effect after operation. The thalamic DBS had a small beneficial effect on the tremor score and the Jebsen score but the IPG had to be removed 11 months after the operation due to an infection. After removal of the IPG the patient still demonstrated an improved tremor score although the performance on the Jebsen test was not altered by this persisting microthalamotomy effect.

Figure b

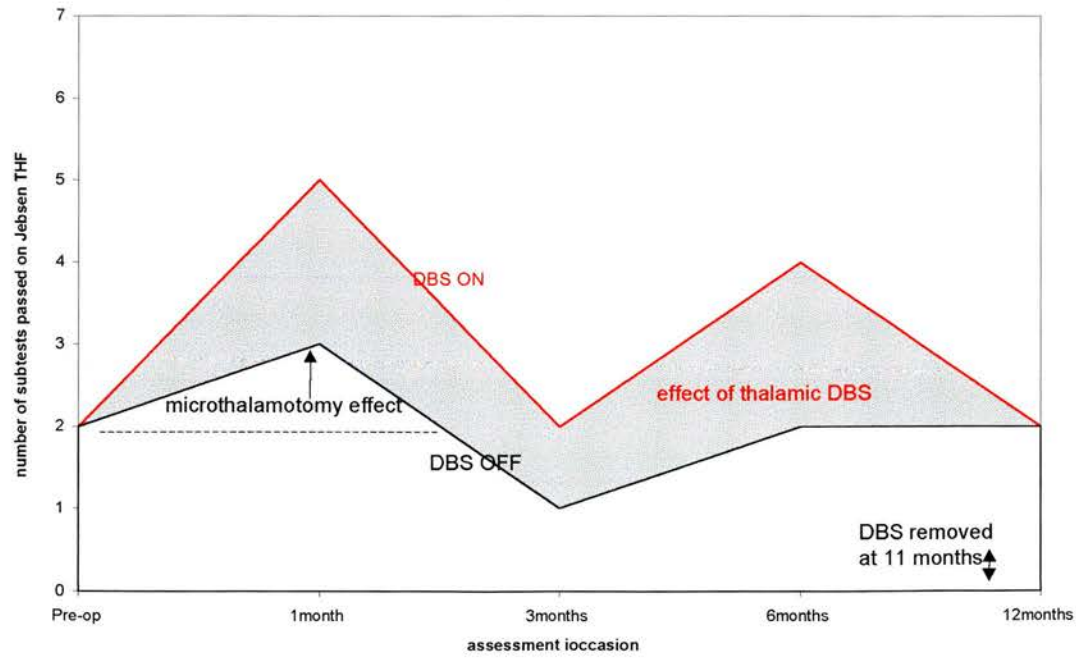
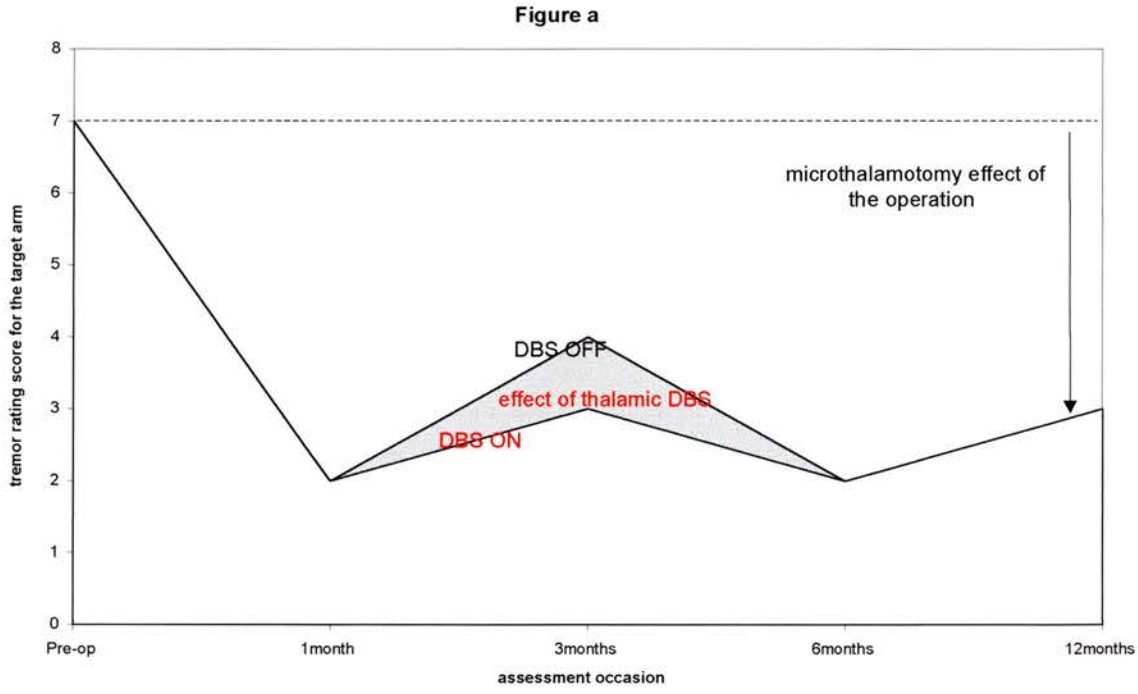


Figure 6-9: Patient 5

A 50 year old woman with MS for 19 years with a movement disorder affecting both of the upper limbs, the head and the trunk. The target arm was the dominant right arm.



This patient showed a considerable microthalamotomy effect which resulted in greatest improvement in the tremor score at the 1 month post-operative assessment. At 12 months after the operation the patient had a lower tremor score and an improved Jebsen score regardless of whether the DBS was on or off.

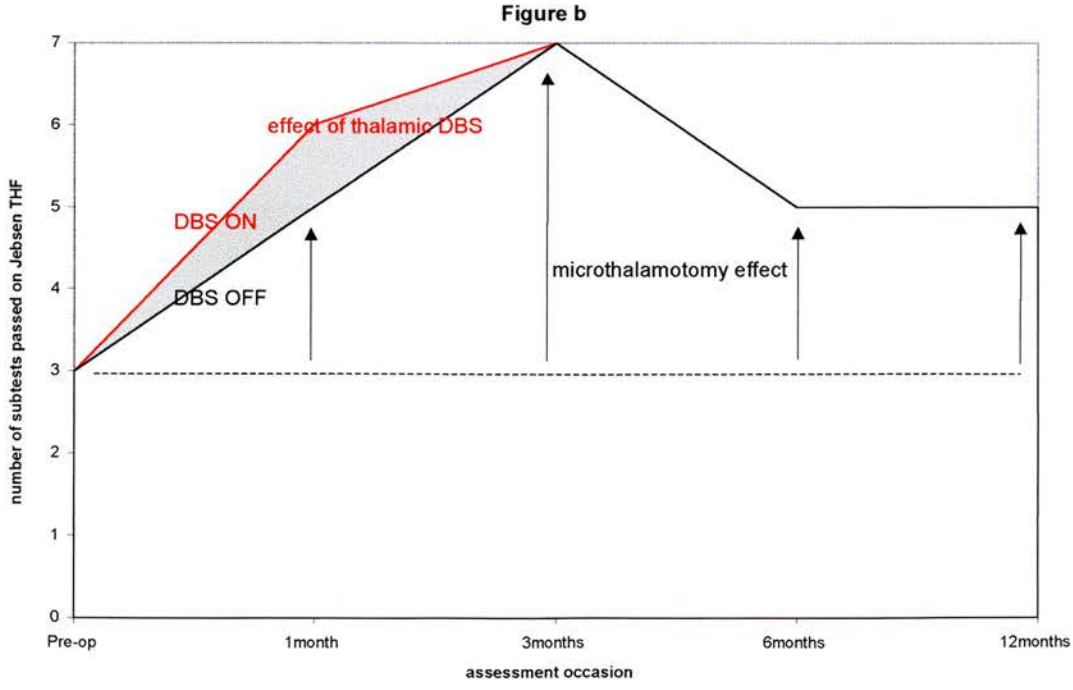
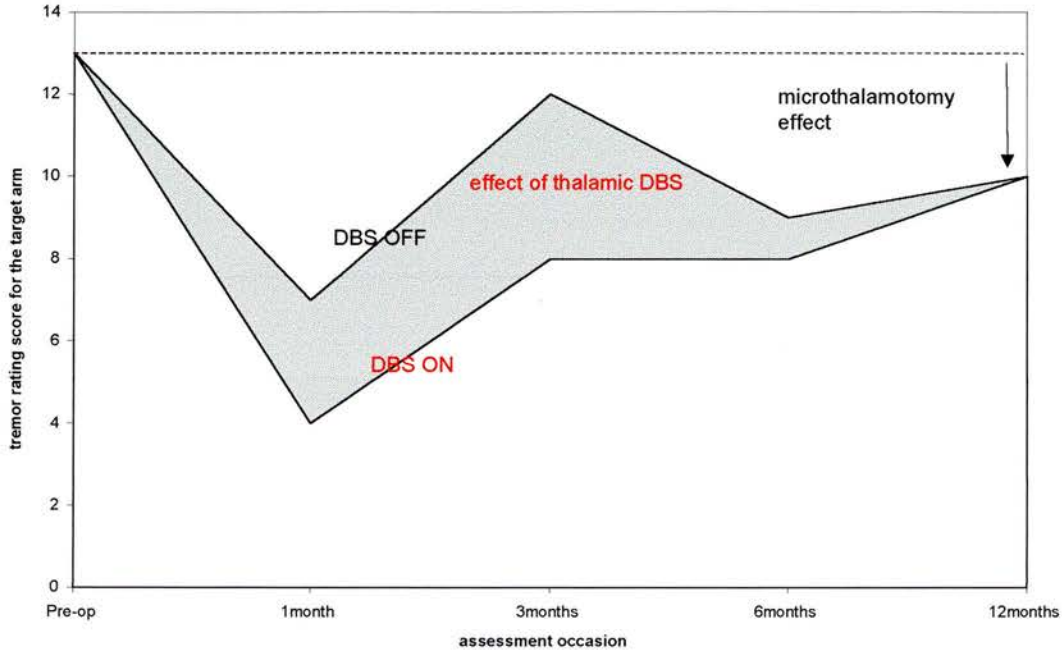


Figure 6-10: Patient 6

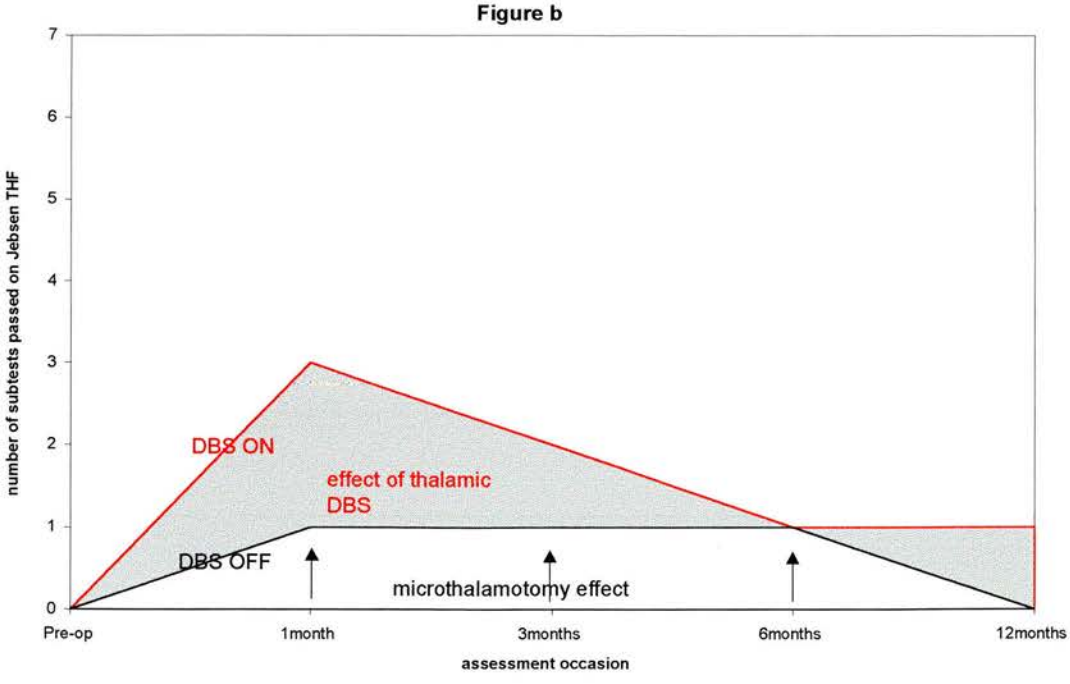
A 37 year old man with MS for 11 years and a movement disorder affecting the upper limbs, the head and trunk. The target arm was the dominant arm.

Figure a



The patient showed a microthalamotomy effect which was present after operation and persisted resulting in a reduction in the tremor score at the 12 month post-operative assessment (it did not influence the Jebsen score). Thalamic DBS had no effect on the tremor score and only a small beneficial effect on the Jebsen score 12 months after operation.

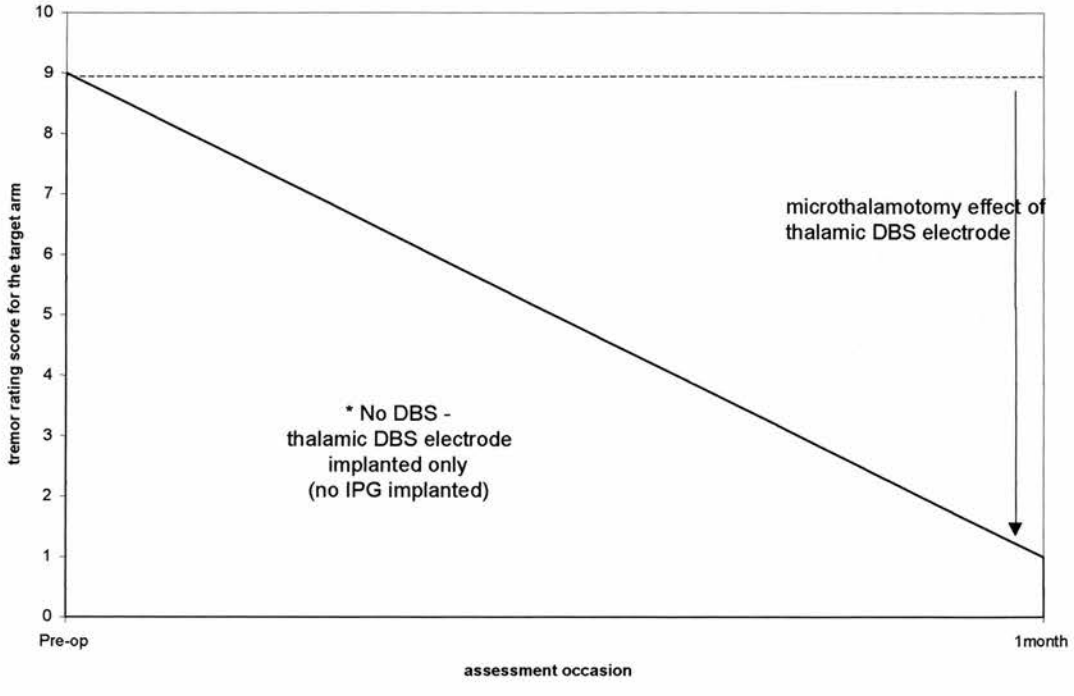
Figure b



Figures 6-11: Patient 7

A 27 year old man with MS for 7 years with a movement disorder for 3 years which affected both of the upper limbs, the head and the trunk.

Figure a



This patient had a marked microthalamotomy effect after implantation of the thalamic DBS electrode and therefore did not proceed to implanation of the IPG. When assessed 1 month after operation the microthalamotomy effect persisted and resulted in an improved tremor and Jebsen scores. The patient refused later follow-up assessments.

Figure b

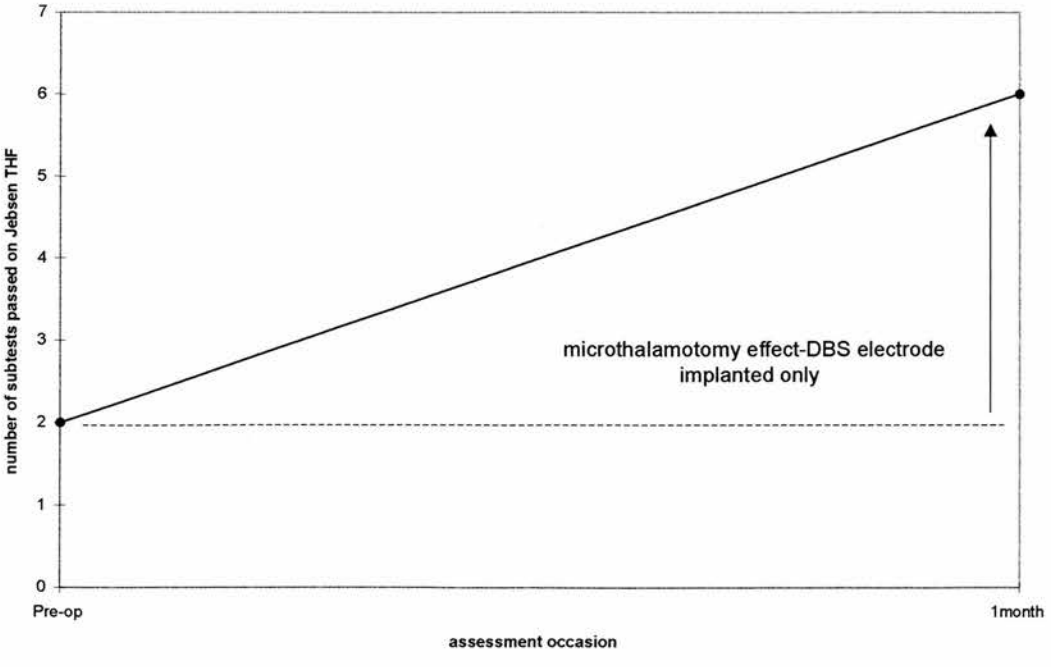
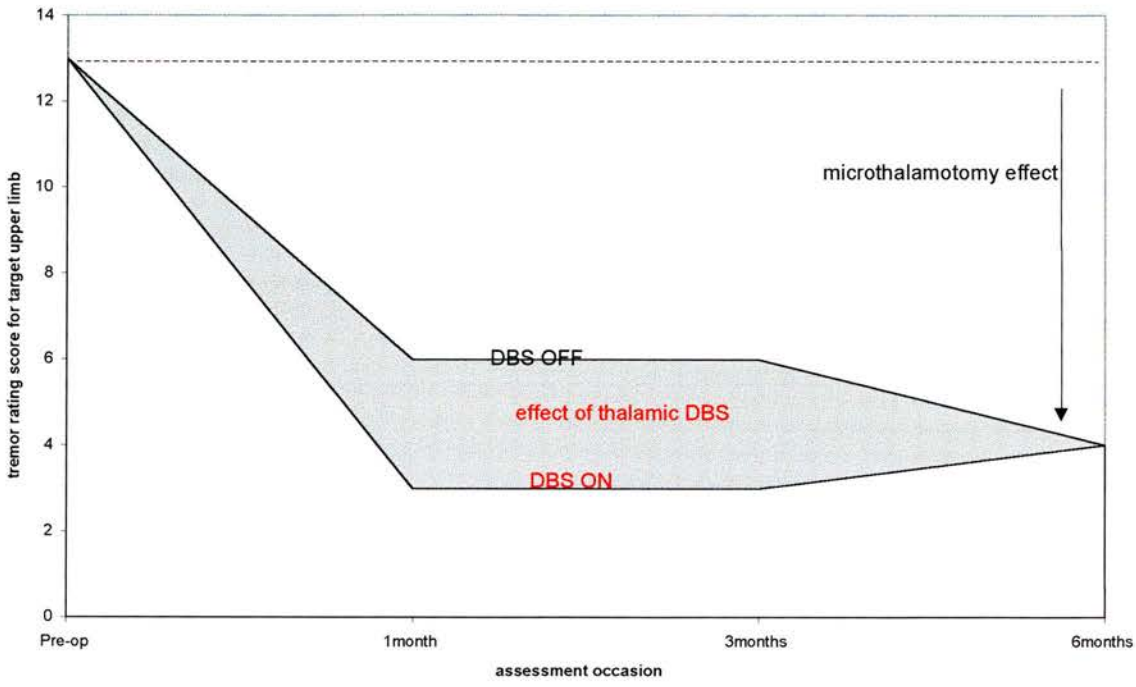


Figure 6-12: Patient 8

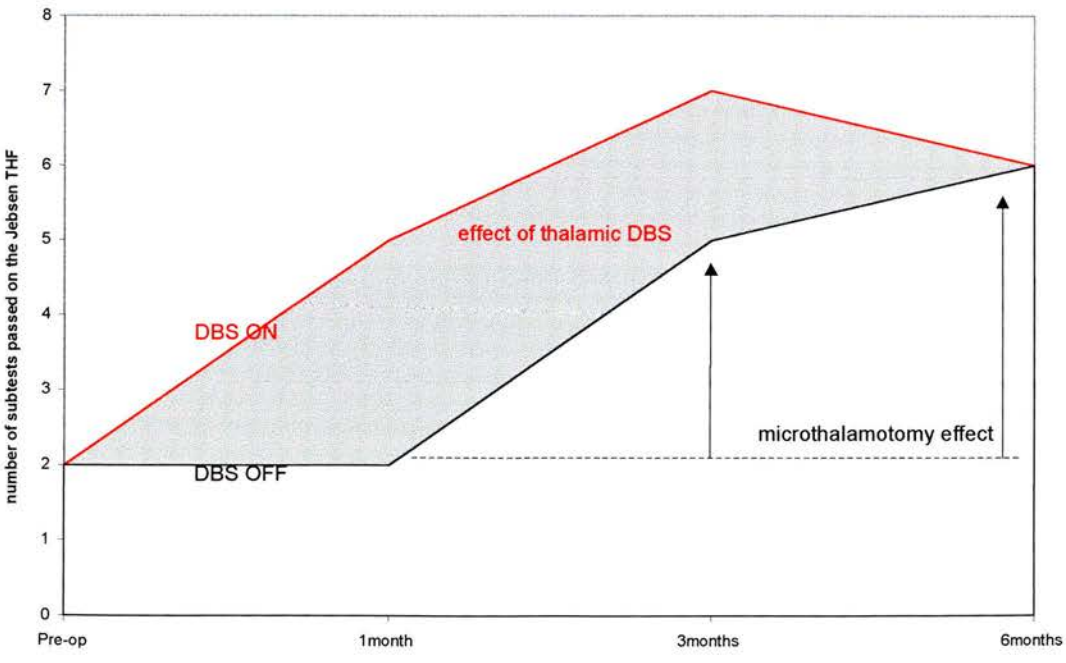
A 44 year old woman with MS for 7 years and a movement disorder for 3 years affecting the upper limbs, the head and trunk. The target arm was the dominant right arm.

Figure a



Patient 8 showed a marked microthalamotomy effect which reduced the tremor score at the 1 month assessment but did not influence the Jebsen score until the 3 month assessment. Thalamic DBS also had a beneficial effect at 1 month and 3months post-operatively but had no effect at 6 months. Twelve month assessment data was not obtained because the patient deteriorated and required admission to hospital. She was unable to be positioned in a chair to be assessed because of severe lower limb spasticity and sacral pressure sores.

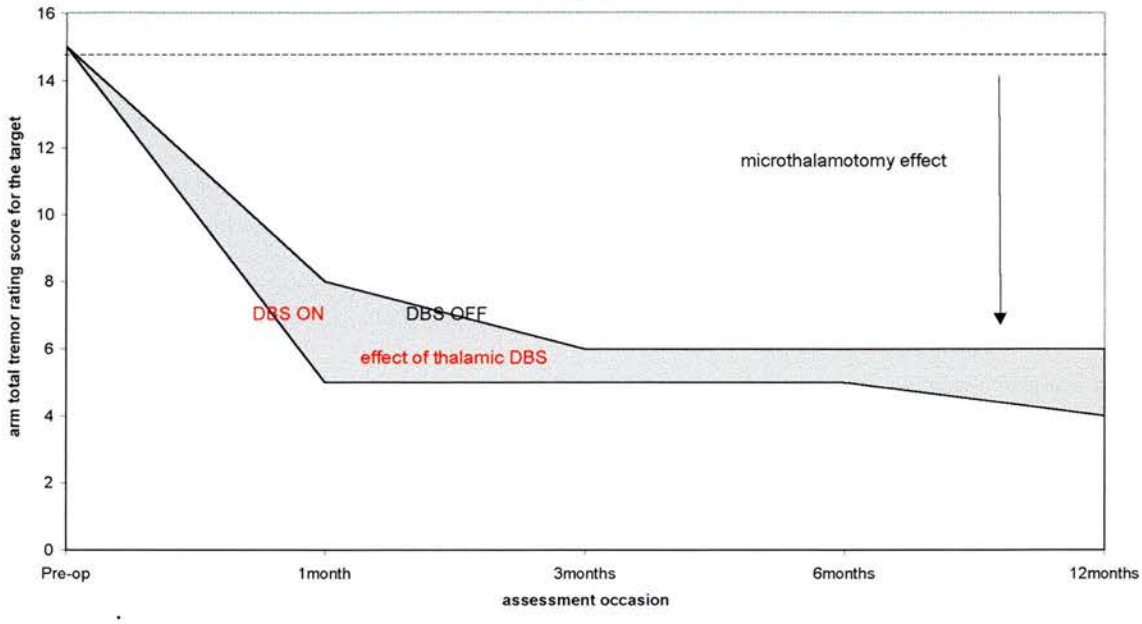
Figure b



Figures 6-13: Patient 9

A 46 year old woman with MS for 16 years and a movement disorder for 5 years which affected the upper limbs, the head and trunk. The target arm was the dominant right arm.

Figure a



This patient had a marked microthalamotomy effect which increased with time and was maximal at the 6 and 12 month assessments. The DBS had a small beneficial effect on Jebsen scores, 1 and 3 months after the operation but the effect was not evident at the 6 and 12 month post-operative assessments. The patient was 'better' when the DBS was off at the 12 month assessment than before the operation which is shown on the video tape of the patient performing the volumetric test with the DBS off and on.

Figure b

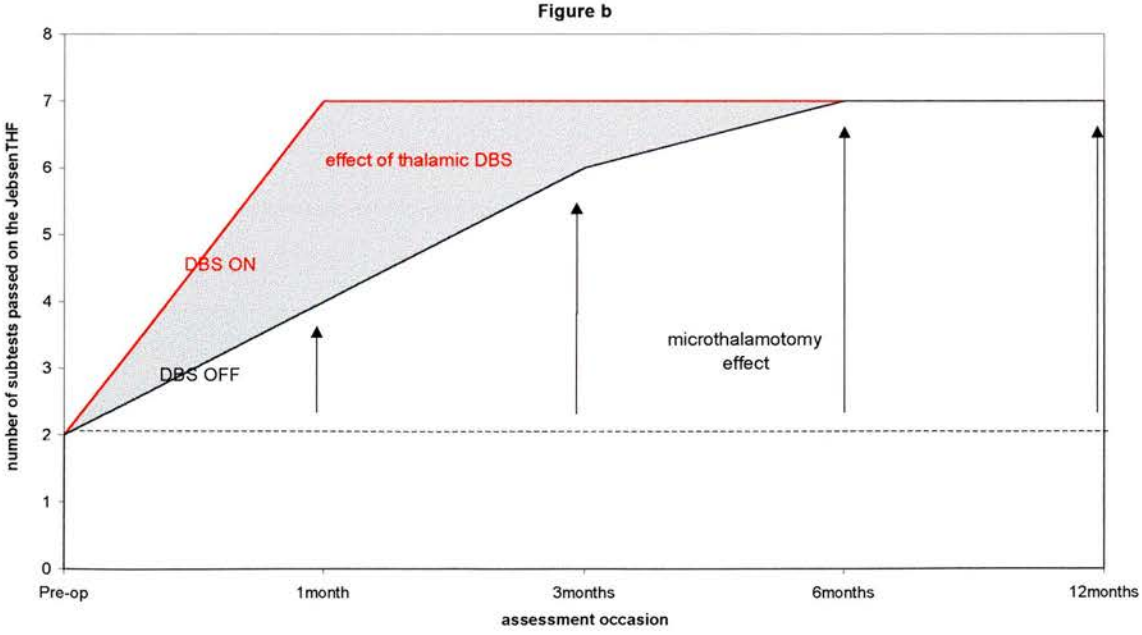
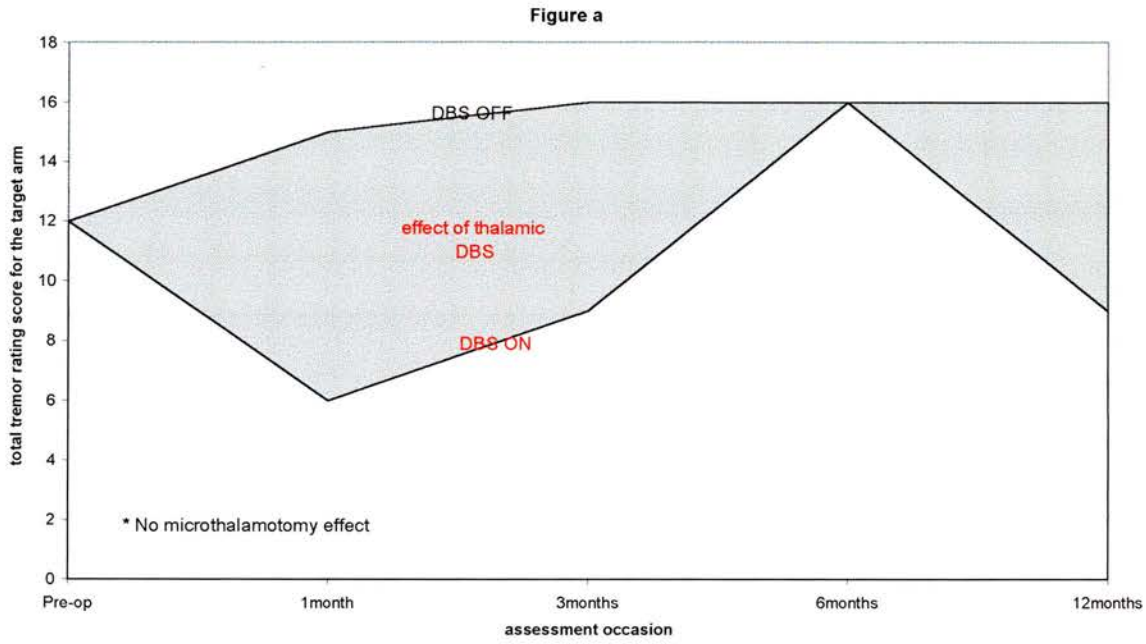
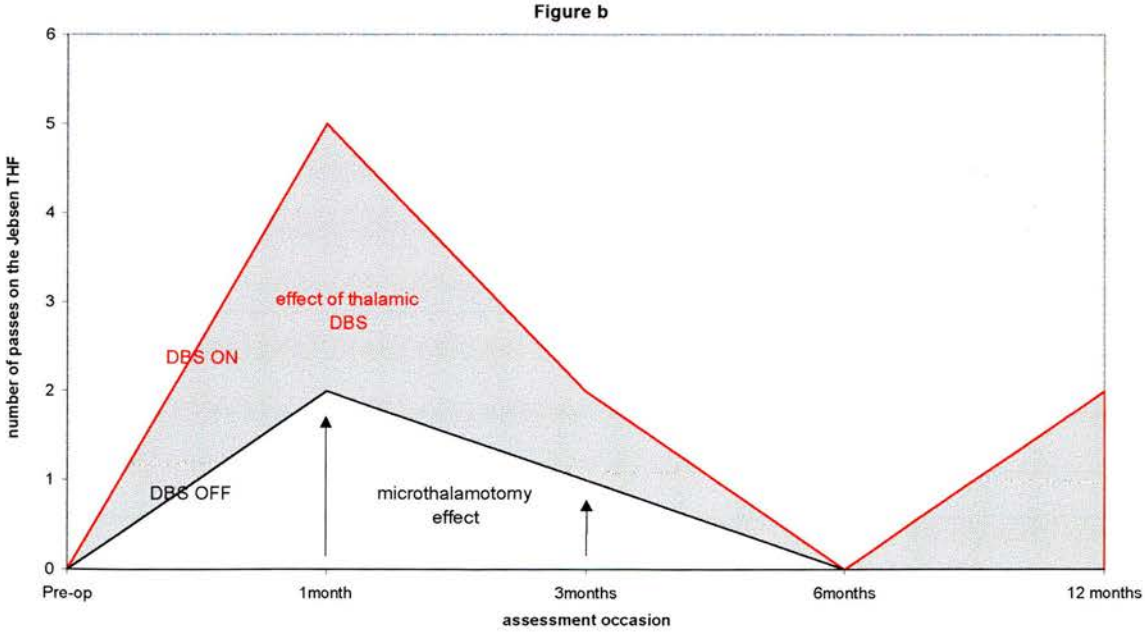


Figure 6-14: Patient 10

A 39 year old man with MS for 10 years affecting the upper limbs, the head and trunk. The target arm was the left dominant arm.



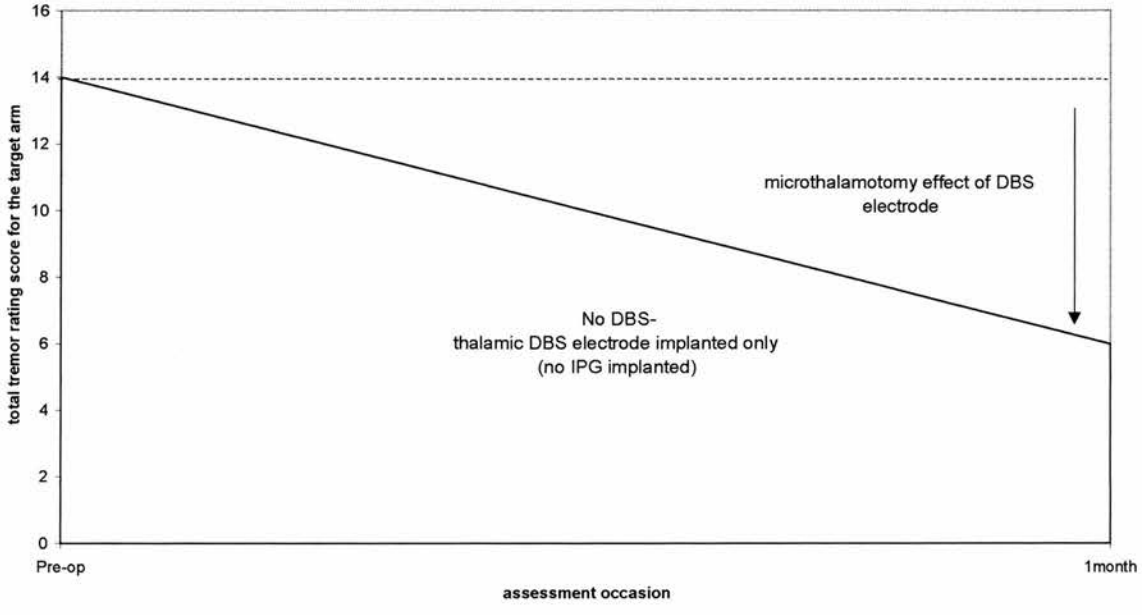
There was no post-operative microthalamotomy effect present when the tremor scores were considered. However, there was a small microthalamotomy effect which improved the Jebsen scores at the 1 and 3 month post-operative assessments. The effect of thalamic DBS was greatest at the 6 month assessment. The DBS was reprogrammed and a small benefit resulted in a reduction in severity of tremor and improved performance on the Jebsen subtests.



Figures 6-15: Patient 11

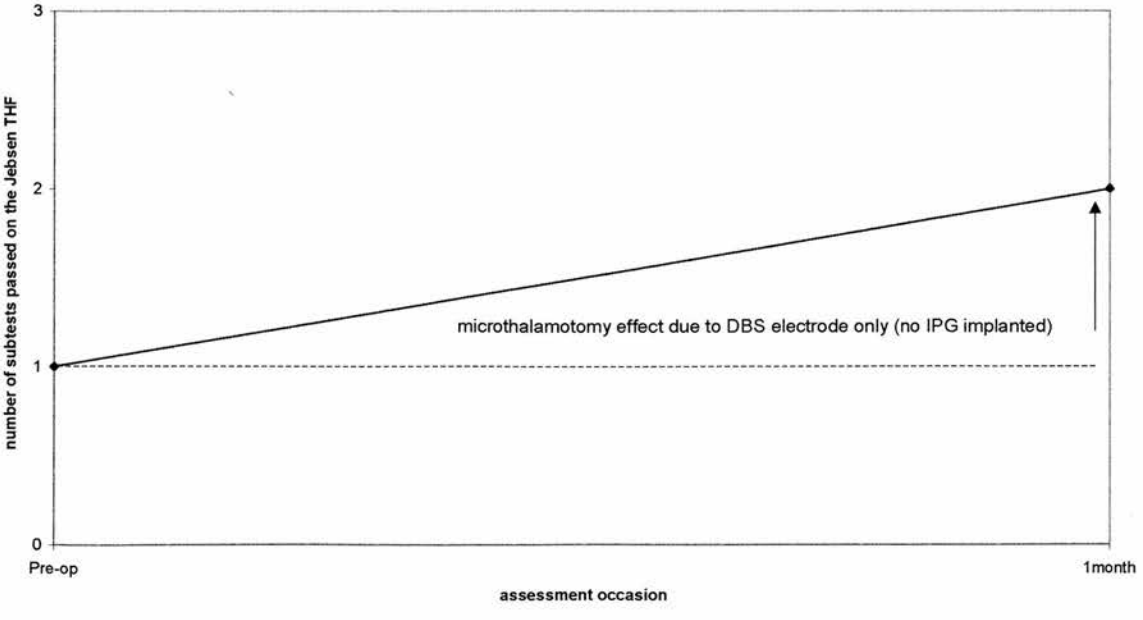
A 42 year old woman with MS for 8 years and a movement disorder affecting the upper limbs, the head and trunk. The target arm was the non-dominant left arm because dexterity was poor in the dominant arm.

Figure a



There was a microthalamotomy effect present after the operation but this patient's functional use of the arm was greatly limited by severe involvement of the head (titubation). This can be seen on the video tape, patient 11 is the patient demonstrating a microthalamotomy effect which may result from the operation.

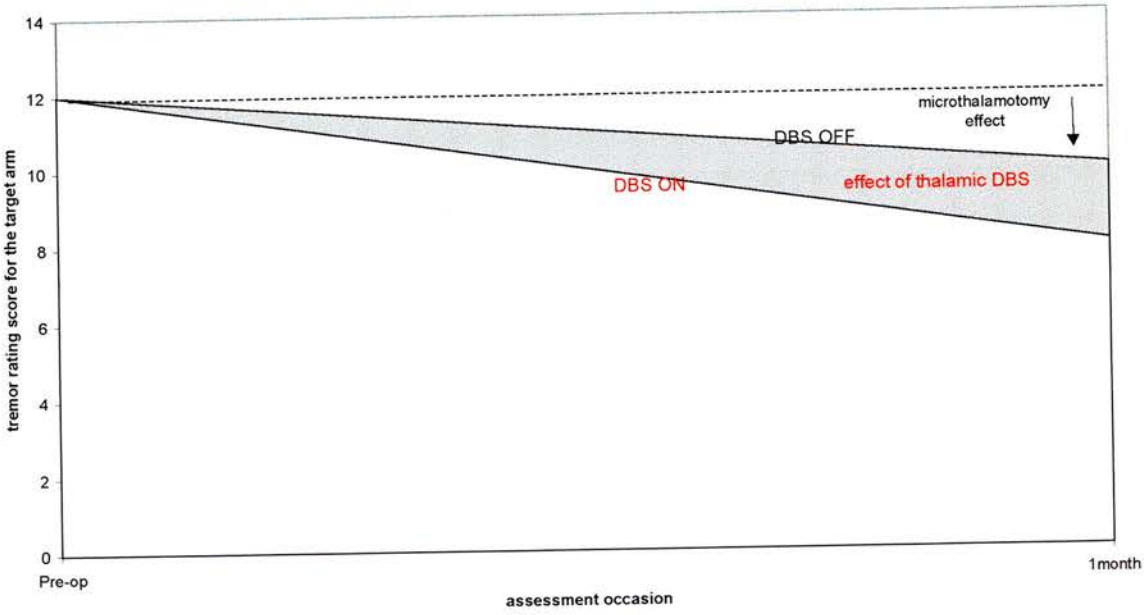
Figure b



Figures 6-16: Patient 12

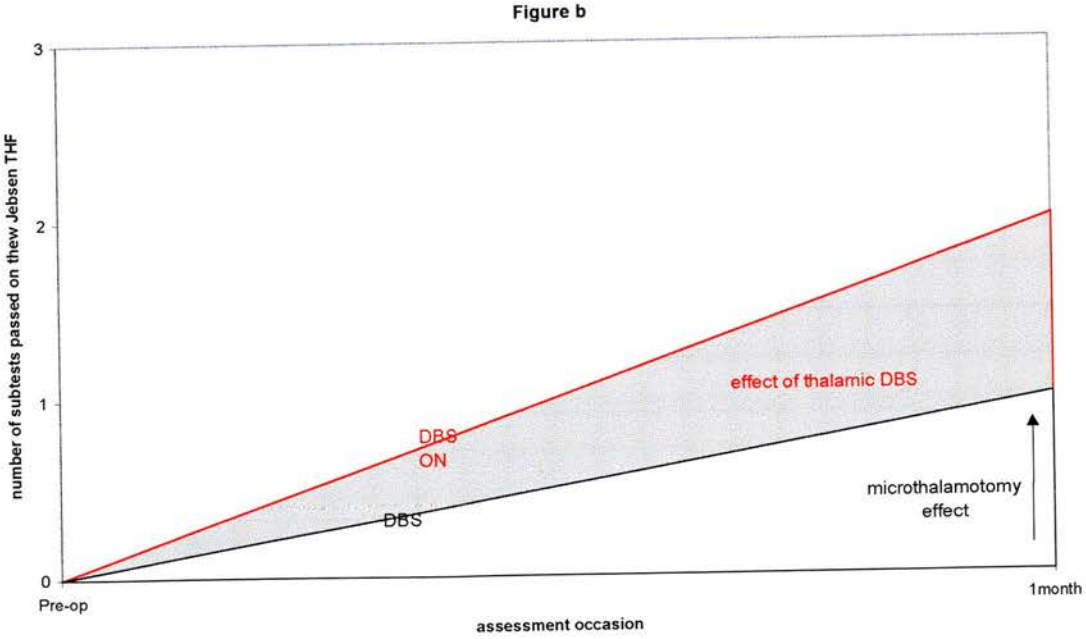
A 51 year old man with MS for 16 years and a movement disorder for 9 years affecting the upper limbs, the head and trunk. The target arm was the non-dominant arm because the function was better preserved in this arm.

Figure a



There was a small microthalamotomy effect with an additional small beneficial effect from thalamic DBS. Optimal programming of the thalamic DBS was limited in this patient by dysarthria which was induced if the amplitude of stimulation was increased beyond a certain threshold.

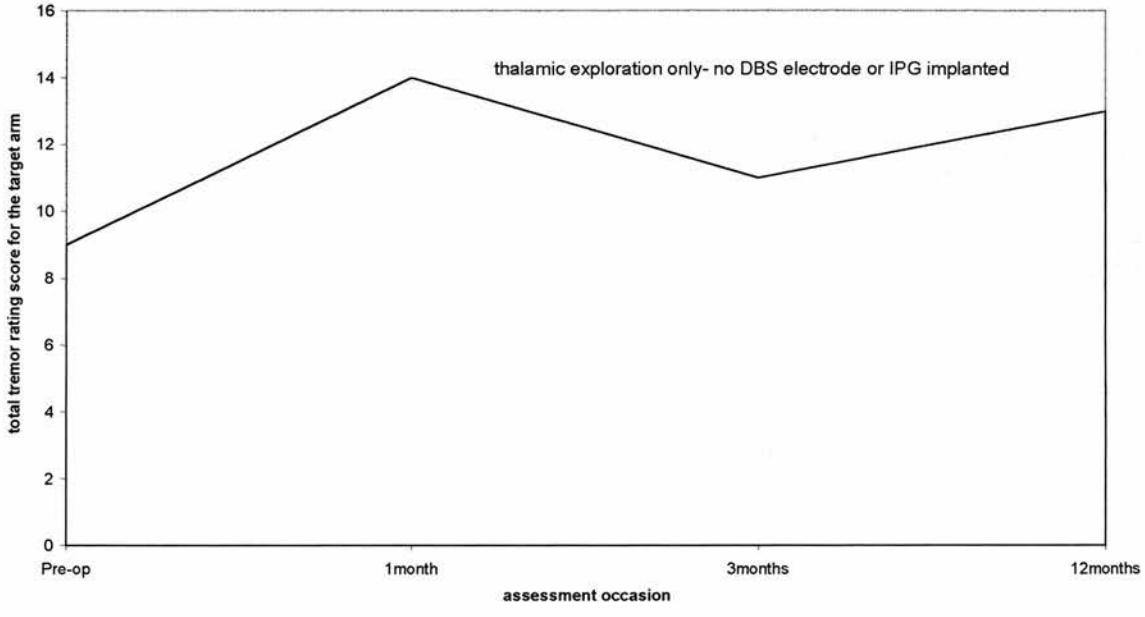
Figure b



Figures 6-17: Patient 13

A 36 year old woman with MS for 6 years and a movement disorder for 5 years which affected the upper limbs, the head and trunk. The target arm was the right dominant arm. Patient 13 had undergone thalamotomy for the same arm 4 years previously.

Figure a



This patient had thalamic exploration performed only. Thalamic DBS was unsuccessful and no target could be found during the operation. Figures a and b show a slight deterioration in severity of tremor and performance on the Jebsen subtests over the 12 months after the operation.

Figure b

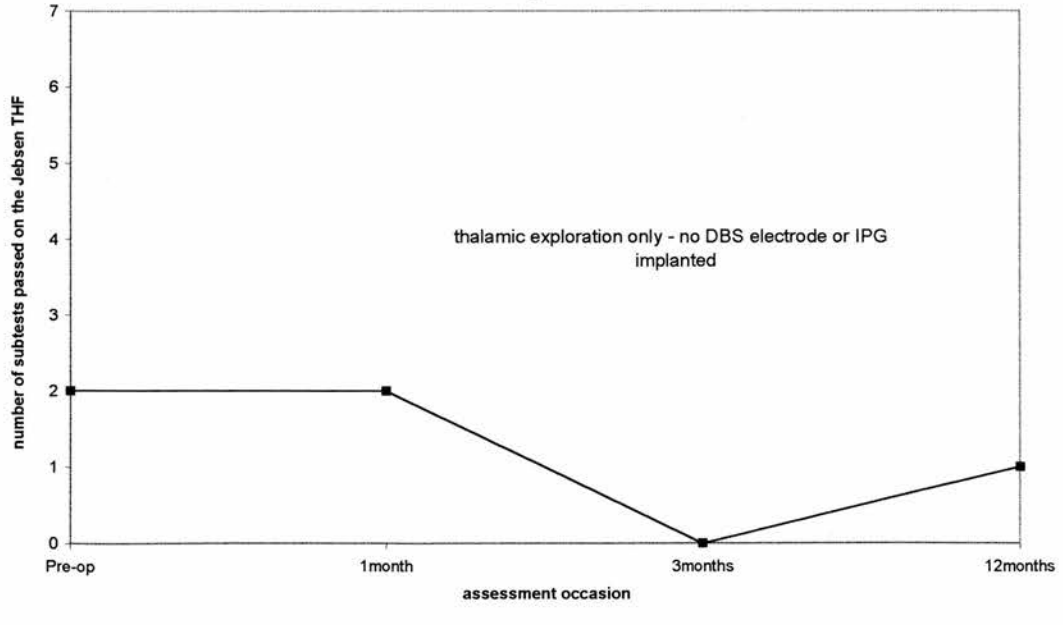
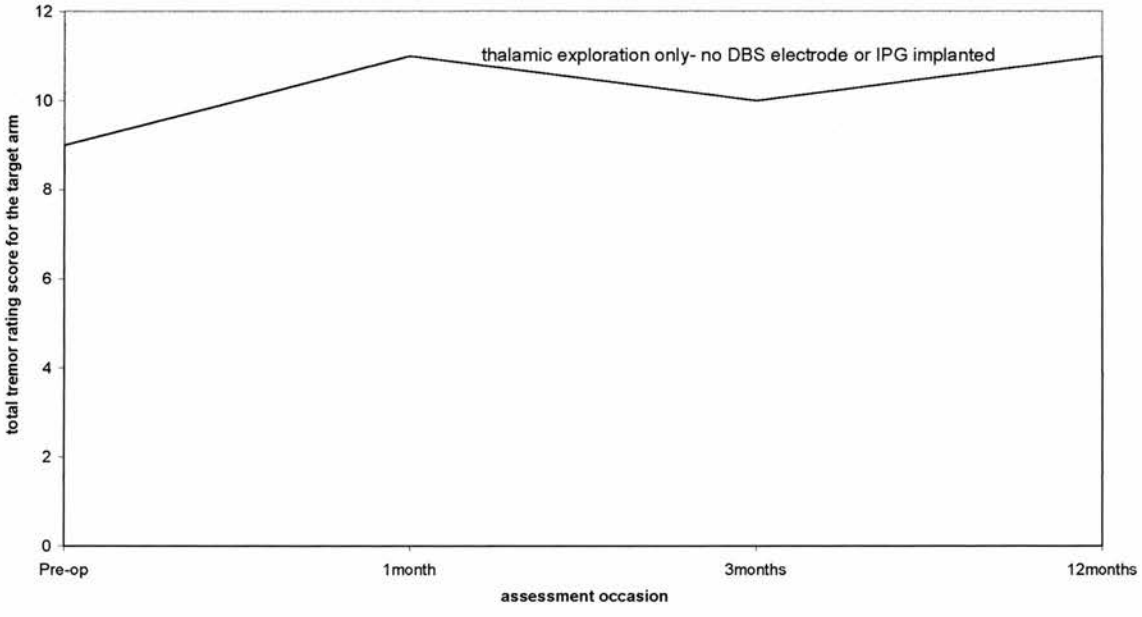


Figure 6-18: Patient 14

A 31 year old man with MS for 15 years and a movement disorder for 3 years affecting the upper limbs, the head and trunk. The target arm was the non-dominant left arm. The patient had undergone thalamotomy 5 years previously for a movement disorder in the right arm.

Figure a



This patient had thalamic exploration performed but did not proceed to implantation of any DBS equipment, as a target could not be found. The figures show little change in the severity of tremor but there was some deterioration in the performance of the Jebsen subtests over the 12 months after the operation.

Figure b

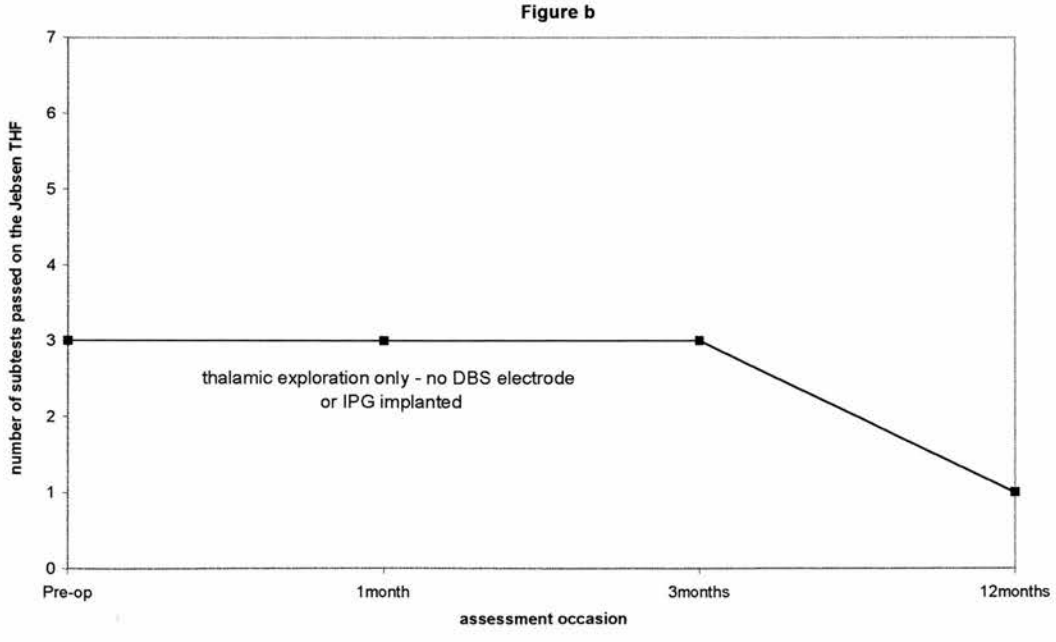
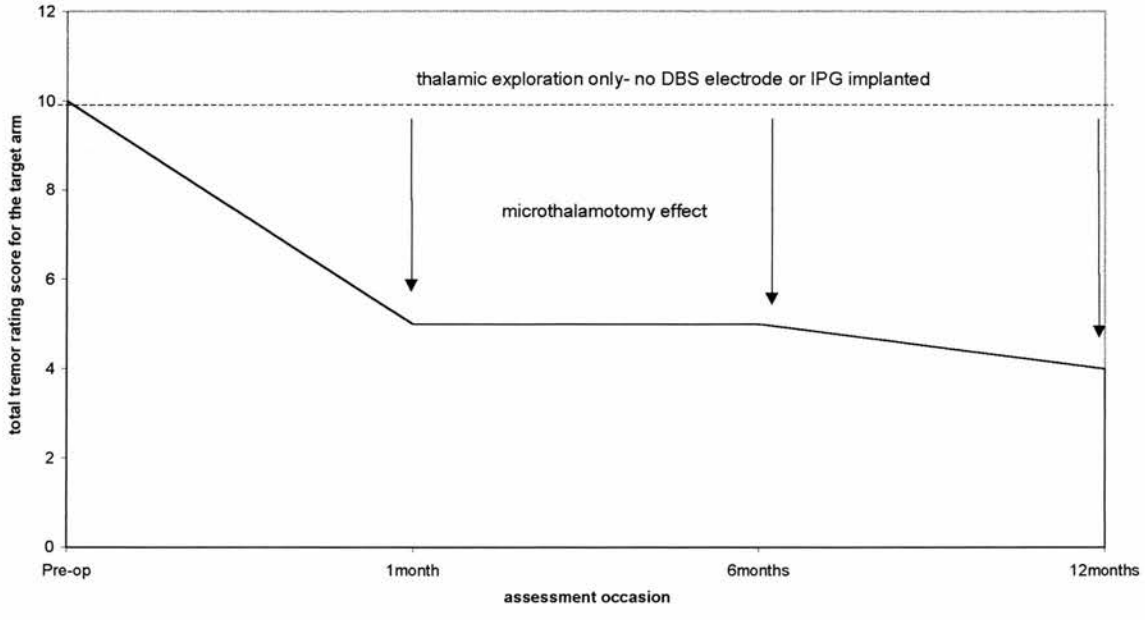


Figure 6-19: Patient 15

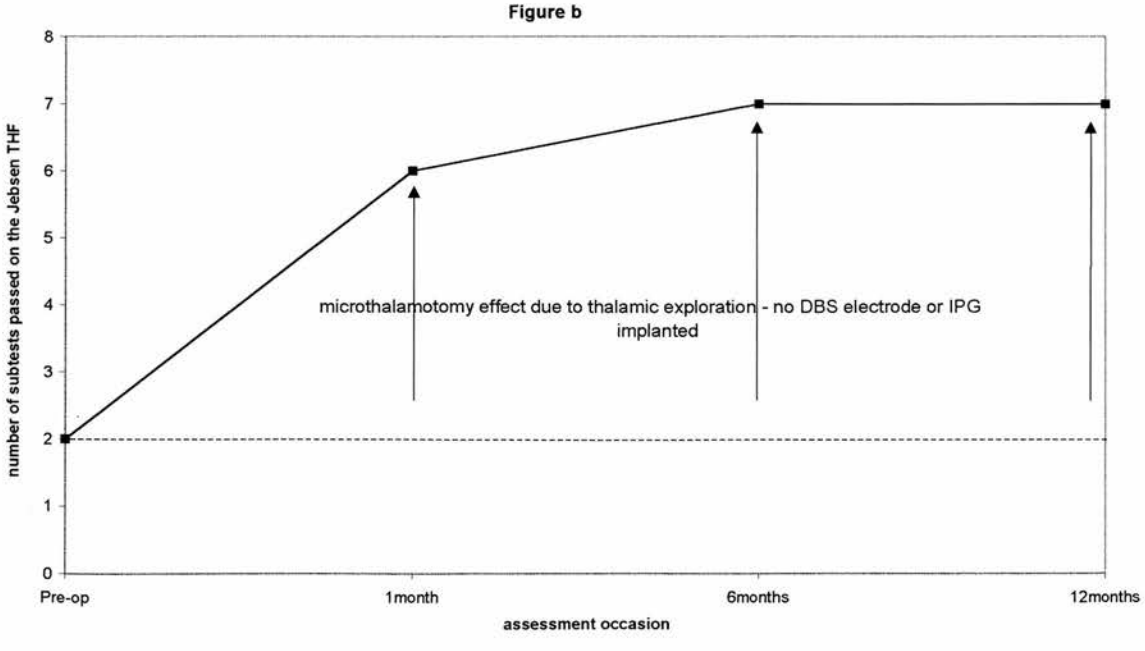
A 51 year old man with MS for 30 years and a movement disorder for 8 years affecting the upper limbs. The target arm was the dominant right arm.

Figure a



This patient had thalamic exploration performed but did not proceed to implantation of any DBS equipment as a target could not be found. The figures show that despite the fact that the operation was regarded as unsuccessful the patient had a marked beneficial microthalamotomy effect after the operation which persisted over 12 months and had a beneficial effect on the tremor score and the Jebsen score.

Figure b



6.5.1 Microthalmotomy effect

Ten of the 15 patients who underwent surgery had an initial microthalamotomy effect after the operation which either reduced the severity of the tremor score in the target upper limb, improved the performance on the Jebsen subtests or had a beneficial effect on both outcome measures. The thalamotomy effect occurred in 7 patients (patients 1, 4, 5, 6, 8, 9 and 12) after implantation of the full DBS system; in 2 (patient 7 and 11) after implantation of the DBS electrode only and in 1 (patient 15) in whom the operation was unsuccessful, after thalamic exploration.

The patients all continued to show a persisting beneficial microthalamotomy effect at the 12 month post-operative assessment although patients 7, 8, 11 and 12 were not formally assessed because of reasons discussed in section 6.2.4 (record of the follow-up assessments).

6.6 Long-term Effects of Thalamic DBS

The long term effects of thalamic DBS were divided up into the effects on impairment, disability, handicap and aspects of QOL. Comparison was made of the scores of the different scales and tests before operation with the scores 12 months after operation in the patients who had implantation of DBS equipment (excluding those who had unsuccessful attempts (N = 3)). The number of patients assessed before operation was 12. However the number of patients assessed at 12 months after operation was smaller because the assessments could not be completed on some patients for various reasons. One patient (patient 4) had the thalamic DBS removed at 11 months. Because of the time limit of the study twelve month follow-up data was not available on the last two patients who underwent operations in Nov 1999 and Feb 2000 (patients 11 and 12). The two patients who suffered thalamic haematomas (patients 7 and 8) were not able to return to DCN for reassessment at 12 months and therefore it was not possible to complete the Kurtzke FS or the EDSS as a neurological examination was necessary. The assessment forms had to be posted to the patients for completion and patient 7 did not return the forms. The FIM and BI were scored by telephone conversation.

The mean and median values for the measures used in the study are shown in the following tables. The level of significance between the scores of the measures before operation and the scores 12 months after operation using the Wilcoxon signed ranks

test are also shown (in patients assessed on both occasions). P<0.05 was the level accepted for significant difference.

6.6.1 Effects on impairment/ disability

The Kurtzke Cerebellar FS and the EDSS were scored. No significant change was found between the assessments before operation and 12 months after although the scores of both the Kurtzke Cerebellar FS and the EDSS were worse at the 12 month follow-up assessment than they were pre-operatively.

Table 6-9: Details on the Kurtzke Cerebellar Functional Systems and the EDSS

	N	Mean	Median	P value
Kurtzke FS (cerebellar)				
Best possible score = 5	Pre-operative = 12	4.2	4.5	0.16
Worst possible score = 0	12 m after operation = 7	3.9	4	
EDSS				
Best possible score = 0	Pre-operative = 12	7	7	0.32
Worst possible score = 10	12 m after operation = 7	7.3	7.5	

6.6.2 Effects on disability

6.6.2 (i) FIM and Barthel Index total scores

The total score of the self-care section of the FIM was used to provide a measure of the patient's ability to perform activities of daily living which included eating, grooming, dressing upper body, dressing lower body, bathing and toileting. These ADL covered a range of activities which required the patient to use the target upper

limb. In 6 (67%) of the 9 patients the total score for the self-care section of the FIM was either the same or better at 12 months after operation than before. Three patients showed deterioration in scores (patients 3, 7 and 8).

The Barthel was included as a more global measure of disability to enable a comparison to be made of activities of daily living which were influenced more by general mobility rather than upper limb function. In 7 (78%) of the 9 patients the total Barthel score was either the same or better at 12 months after implantation of DBS compared with pre-operatively. The 2 patients (patients 7 and 8) who showed considerable deterioration in Barthel scores (16 – 5, 15 – 2) both suffered thalamo-capsular haematomas after implantation.

There was no significant difference in the FIM (self-care) ($p = 0.67$) or the Barthel ($p = 0.67$) scores between the pre-operative and 12 month post-operative assessments. The mean and median FIM scores were slightly better at 12 months after operation than before the operation indicating a slight reduction in the amount of assistance that patients required to perform the activities included in the self-care section of the FIM. The mean and the median Barthel scores were lower (the median score being 50% lower) at 12 months after operation than before operation suggesting that the patients' general level of ability in performing ADL had decreased.

Table 6-10: Details on the measurement of disability

	N	Mean	Median	P value
FIM (self-care section)				
Best possible score = 42	Pre-operative = 12	22.9	23.5	} 0.67
Worst possible score = 6	12 m after operation = 9	23.7	24	
Barthel Index				
Best possible score = 20	Pre-operative = 12	10.3	13	} 0.67
Worst possible score = 0	12 m after operation = 12	9	6.5	

6.6.2 (ii) FIM and Barthel Index items

As deterioration in one item of the FIM or Barthel in a particular patient could be counteracted by improvement in another resulting in the total score remaining the same it was necessary to look at changes in individual items for each patient.

There was some improvement in all items of the self-care section of the FIM but especially for the dimensions of eating (7 patients improved) and grooming (4 patients improved). The feeding dimension of the BI also showed improvement in 3 patients, dressing in 1 and toileting in another patient because he was able to perform intermittent self-catheterisation independently after implantation.

The 2 patients (patients 7 and 8) who suffered thalamo-capsular hemipareses post-opertively showed deterioration in items of both the FIM and the Barthel as the motor weakness resulting from the hemiparesis not only limited the functional ability to perform activities of daily living with the target upper arm but also had a severe impact on their ability to perform more general activities of daily living such as

transfers, bathing and walking. Both patients developed problems with incontinenece due to their reduced levels of mobility.

Table 6-11: Change in FIM (self-care) and Barthel Index scores from pre-operative assessment to 12 month follow-up (N = 9)

FIM	Dimension:	No change	Improved	Deteriorated
	Eating	3	7	1
	Grooming	5	4	2
	Bathing	7	1	2
	Dressing upper body	5	2	3
	Dressing lower body	4	3	3
	Toileting	5	2	3
Barthel	**Dimension:**	**No change**	**Improved**	**Deteriorated**
	Bowels	9		1
	Bladder	6	1	3
	Toileting	8		2
	Feeding	7	3	
	Transfer	8		2
	Mobility	8		2
	Dressing	7	1	2
	Stairs	9		1
	Bathing	8		2

6.6.3 Effect on handicap

The LHS and the Handicap Questionnaire were the 2 scales used in the study to estimate change in handicap due to thalamic DBS. There was no significant change in handicap experienced by the patients 12 months after operation compared with before the operation.

Table 6-12: Details on the measurement of handicap

	N	Mean	Median	P value
LHS				
Best possible score = 100	Pre-operative = 12	57.1	57.5	} 0.32
Worst possible score = 0	12 m after operation = 8	54.1	54.5	
Handicap Questionnaire				
Best possible score = 0	Pre-operative = 12	6.6	6.5	} 0.10
Worst possible score = 9	12 m after operation = 8	6.9	7	

6.6.4 Effects on aspects of QOL

The only significant change between the scores before operation and 12 months after operation were in the anxiety score of the HAD. Patients perceived themselves to be less anxious 12 months after operation compared with before the operation (p = 0.03) However the number of people assessed at 12 months was small (N = 8).

Table 6-13: Details on measurements of aspects of QOL:

	N	Mean	Median	P value
Fatigue Severity Scale				
Best possible score = 1	Pre-operative = 12	5.1	5.4	0.34
Worst possible score = 7	12 m after operation = 8	5.4	5.4	
HAD				
Best possible score = 0	Pre-operatively = 12	14.8	13	0.18
Worst possible score =42	12 m after operation = 8	9.4	5	
HAD (anxiety)				
Best possible score = 0	Pre-operatively = 12	7.5	7	0.03
Worst possible score = 21	12 m after operation = 8	4.4	3	
HAD (depression)				
Best possible score = 0	Pre-operatively = 12	7.3	6	0.49
Worst possible score = 21	12 m after operation = 8	5	3.5	

6.6.5 Effects on percentage of functional disability

The percentage functional disability score was calculated by expressing the patient's total upper limb score as the sum of Parts A, B and C of the MFTRS in % terms as suggested by Fahn{Fahn et al. 1988). The figure given in the column headed 'change' is simply the pre-operative % minus the 12 month % and is not a ratio.

Table 6-14: The percentage functional disability between pre-operative and 12 month evaluations

Patient	Pre-operative	12 month follow-up	change
1 ♣	75%	58%	17%
2 ♣	72%	45%	27%
3 ♣	78%	68%	10%
4 ♣	75%	68% (DBS removed at 11 months)	7%
5 ♣	68%	52%	16%
6 ♣	88%	83%	5%
7 (♦)	63%	not assessed owing to geographical limitation	
8 ♣	78%	DNA	
9 ♣	87%	28%	59%
10 ♣	85%	77%	8%
11 (♦)	70%	not assessed owing to time limit	
12 ♣	75%	55% (*1month-op Feb2000)	20%
13 (#)	73%	78%	5%
14 (#)	78%	87%	11%
15 (#)	75%	48%	27%
Mean	**76%**	**68%**	**18%**

♣ = DBS system implanted (DBS electrode and IPG)
♦ = DBS electrode implanted
= Unsuccessful attempts

The change in percentage functional disability ranged from 5 – 59% overall (mean score = 18%) when all 15 patients were considered. In those patients in whom DBS were implanted 50% of patients change scores fell between 8 – 20% and there was one outlying change score of 59% in patient 9. One of the patients (patient 15) in whom a thalamic target could not be located intra-operatively (therefore regarded as

an unsuccessful attempt) had a marked improvement in the change in percentage of functional disability (change of 27%) at 12 months, despite the fact that no DBS equipment was implanted.

6.6.6 Patients' perceptions of the outcome of the operation

When asked about their opinion of the operation the patients expressed varying degrees of satisfaction as shown in table 6-15. None of the patients were enthusiastic about the outcome of the operation. The five patients who were negative about the outcome of the operation were the three patients in whom the surgeon was unable to locate a target (unsuccessful attempts in patients 13, 14 and 15), the patient who suffered a thalamic haematoma immediately after operation (patient 7) which resulted in hemiparesis and some memory dysfunction and a patient who had a marked beneficial effect on the severity of tremor in the upper limb after implantation of the DBS electrode due to microthalamotomy effect but perceived no benefit as the movement disorder also affected the head and severe head titubation persisted after operation which negated the benefit in the upper limb. The opinions of the last 2 patients who underwent surgery in November 1999 (patient 11) and February 2000 (patient 12) are included despite the fact that only a short period of time had elapsed.

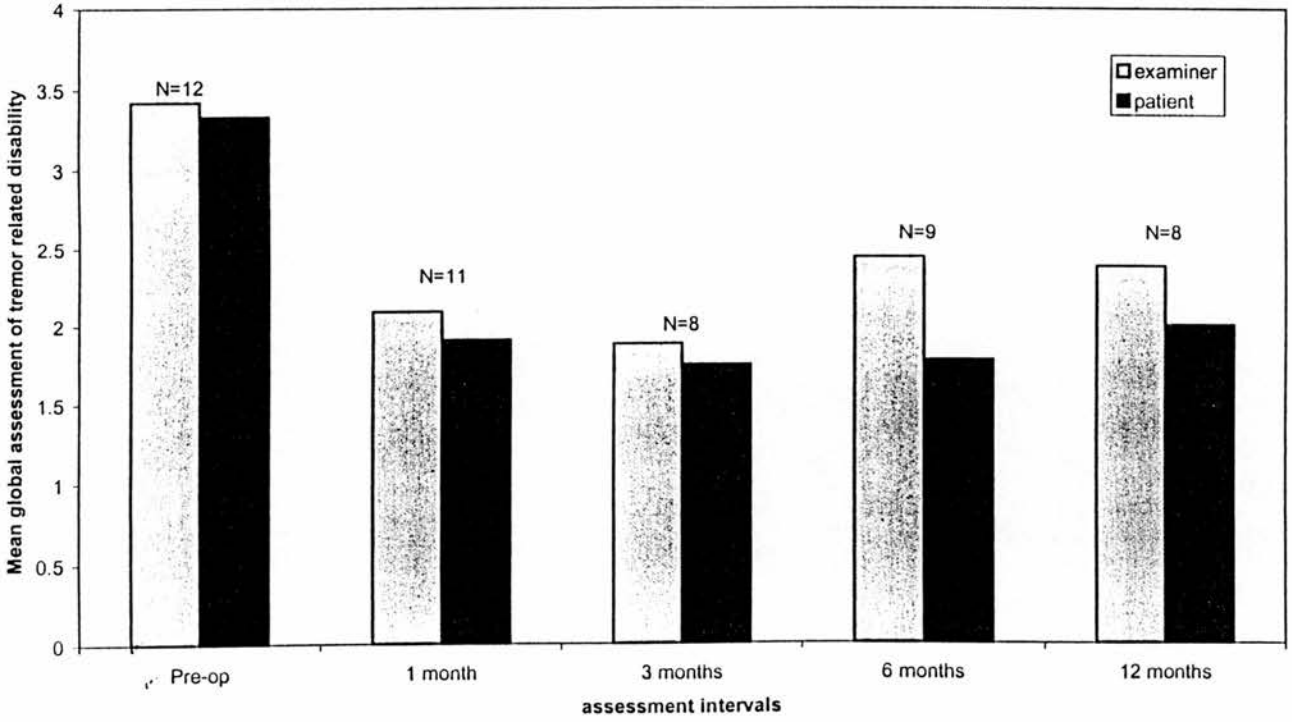
Table 6-15: Patients' perceptions of the outcome of the operation (N = 15)

Patients' opinions	N
Enthusiastic	-
Satisfied	4
Moderately positive	6
Negative	5*
Total	15

6.6.7 Differences between the overall assessment of the examiner versus that of the patient of tremor related disability postoperatively

Both the patients (excluding the 3 who were unsuccessful attempts and did not have any DBS equipment implanted) and the examiner tended to rate the patient's tremor related disability as less severe after surgery than before. The figure shows that at every evaluation the tremor related disability as rated by the patient and compared to that of the examiner differed, patients' ratings of (their) disabilities tending to be marginally less severe than the examiner's ratings.

Figure 6-20: Mean global assessment of tremor-related disabilities by the examiner and patients at all evaluations



6.7 Cost-Effectiveness of Thalamic DBS

The operations performed in this study were carried out between October 1996 and February 2000. Fifteen patients underwent stereotactic exploration of the thalamus, 10 patients had implantation of the DBS system, two patients had implantation of the stimulating electrode only and in three patients the surgeon was unable to locate a target for DBS and the procedure was abandoned. The costs involved in thalamic DBS were categorized into three main areas of interest: the cost of assessment, the cost of the intervention and the cost of follow-up.

6.7.1 Costs involved with thalamic DBS

6.7.1 (i) Assessment costs

The patients were referred to the neurosurgeon to be assessed for their suitability for implantation of a thalamic DBS. The patient was then seen as an outpatient, for an initial consultation in the out-patient clinic of the Department of Clinical Neurosciences which cost £84. If deemed an appropriate candidate they were then admitted at a later date to the Astley Ainslie Hospital so that extensive baseline assessments could be carried out. These assessments were carried out over a two-day period, which necessitated an overnight stay on the rehabilitation ward in Charles Bell Pavilion costing £127.37 which included all staff costs. The subtotal cost for the initial assessments was £211.37 per patient.

6.7.1 (ii) Intervention costs

There were substantial equipment costs associated with this procedure which were not incurred in this study as the MS Society funded the provision of the hardware, the cost of which is approximately £7,000 (£715 for the thalamic stimulation lead, £135 for the extension wire and £6,160 for the pulse generator (costs provided by Medtronic 1998).

Prices were calculated for operations as an average charge (average specialist tariff). In calculating this average charge several factors are taken into account: these were the type of operation (each operation having a procedure code provided by the Office of Populations and Consensus), the average length of stay for that particular operation, consumables utilised (syringes, food, drugs), staff salaries and time and overheads incurred by the unit. The average length of stay for a stereotactic operation was 7 days (information provided by the Information and Statistics Division, NHS in Scotland).

However, all patients who had surgery in this study except those patients who were unsuccessful attempts stayed in DCN longer than 7 days: the mean length of stay was in fact 15 days. Therefore in order to reflect this extra cost incurred to the hospital due to a longer stay in DCN for thalamic DBS, the cost of the additional days was calculated by multiplying the number of additional days exceeding the 7 allowed for stereotacic operation by the cost of one nights stay in hospital (£127.37/night).

Thalamic DBS was a new technique and was being performed in only a small number of cases so the Finance Department in the Trust included it under the code

for stereotactic operations (code AO3). The charge for operation included under this code was £4,602 (provided by the local NHS Trust finance directorate). However if the patient had thalamic exploration performed without the implantation of any equipment (as was the case in those patients in whom DBS was unsuccessful), or had implantation of a thalamic DBS electrode only (as was the case in those patients who had a microthalamotomy effect as a result of the surgery) the charge was £1,982.

Therefore the intervention cost for implantation of the thalamic DBS system was £11,602 (ie. full equipment costs + charge of £4,602 for in-patient stay in DCN); the cost for DBS electrode implantation was £2,697 and the cost for thalamic exploration was £1,982 (ie reduced equipment costs + reduced charge for shorter in-patient stay in DCN).

6.7.1 (iii) Follow-up costs

It became apparent that some of the patients required a short period of intensive training of their target upper limb post-operatively. This was organised on an in-patient basis in the majority of cases at the Astley Ainslie Hospital. Also some patients required more general intensive rehabilitation to return to their preoperative level of functional ability. The charge for rehabilitation was £127.37 per day. The mean length of stay (LOS) for all 9 patients who had a period of rehabilitation was 54 days (median 25 days). Three patients had exceptionally long stays due to the development of post-operative complications. Patients 7 and 8 developed thalamic haemorrhages and patient 4 had a grand mal seizure. Patients 5 and 6 were the most severely disabled patients who were referred for thalamic DBS and were maintained

at home owing to maximum care provided by both Social Services and private care organisations. Both patients had regular respite admissions to the Young disabled Unit at Liberton Hospital and consequently they were transferred there post-operatively to receive a short period of rehabilitation focusing on retraining of the target upper limb. This was followed by an extended period of respite care whilst the support from the various care organisations was restarted before final discharge home. Consequently there was an unforeseen general rehabilitation cost incurred in some patients which turned out to be quite substantial in some cases.

The researcher often had to make frequent visits to the rehabilitation hospitals during the first month following the operation as it was often necessary to carry out some "fine tuning" of the stimulation parameters to achieve the optimum effect. The cost for these visits was £19 per hour{Netten & Dennett 1996). Readjustments of the IPG parameters were made, as needed during scheduled study visits or during interim visits either of the patient to the hospital or of the research fellow to the patient's home where distance allowed. The number of visits for reprogramming varied between patients (range 2 to 14) but the average number of visits was 5.

Also, there were difficulties encountered by the patients and the nursing staff with regard to swiping the IPG with the magnet in order to turn the thalamic DBS on and off. Patients were often not sure whether they had swiped the IPG successfully or not and whether the DBS stimulator was switched on or off. The only solution to this problem appeared to be to issue each patient with a small transistor radio, which produced a buzzing sound (caused by interference of the radio waves) if held over

the IPG when it was switched on. The cost of purchasing the radios (which cost £20 each) was a cost which had not been anticipated at the outset of the study.

The patients were required to attend for review at one, three, six and twelve months post-operatively. The follow-up assessments took place at the Astley Ainslie Hospital where the patient attended as a day case and stayed on the ward for the day so that the assessments could be carried out in the morning and afternoon. There was an obvious direct cost to the NHS for these follow-up assessments (£73.50 /assessment x 4 = £294).

6.7.1 (iv) Additional costs

Transport costs to and from the Western General Hospital and the Astley Ainslie Hospital are mentioned because in some cases, for example in patients living in England, these costs were high. There was a standard scale of charges for ambulance journeys of £20 per hour and £7.55 per mile which was based on area in Scotland and on distance in England. There was also an additional charge of £20 per hour for providing a 2-man crew, which was mandatory for long distance journeys from England.

The procedure involves an ongoing maintenance cost as the patients required to be monitored for any adverse side effects related to the stimulation. Also at some stage the IPG battery will need to be replaced depending on the life expectancy of the patient. There will therefore be additional follow-up costs if patients survive more than 4 or 5 years.

Table 6-16: Length of stay (LOS) in DCN, length of stay in rehabilitation unit (Rehab), number of follow-up visits to reprogram DBS and cost of rehabilitation

Patient	LOS DCN (days)	LOS Rehab (days)	Number of visits by PT to reprogram thalamic DBS	Number of follow-up assessments
1 (♣)	7	14	14	4
2 (♣)	16	14	5	4
3 (♣)	7	7	3	4
4 (♣)	19	68	2	4
5 (♣)	10	43	6	4
6 (♣)	21	25	2	4
7 (♦)	9	253	0-Electrode only	1
8 (♣)	41	103	2	4
9 (♣)	11	–	2	1
10 (♣)	12	10	5	4
11 (♦)	10	–	0-Electrode only	1
12 (♣)	12	–	0	1
Mean	15 days	54 days	4.5 visits	3 visits
Median	12days	25days	2.5 visits	4 visits
13 (#)	5	-	-	4
14 (#)	5	-	-	4
15 (#)	5	5	-	4

6.7.1 (v) The average cost per patient implanted with a thalamic DBS

The average cost per patient implanted with a thalamic DBS was £14,279.65. This figure estimates the total costs for the entire programme of assessment, intervention and follow-up including the costs for assessment of 22 patients who were assessed as not suitable candidates for operation and the costs involved in treating those patients in whom DBS electrodes only were implanted (♦) and those who were unsuccessful attempts (#).

The substantial equipment costs were met by the MS Society in this study. The hardware, (thalamic stimulation lead, extension wire and pulse generator) associated with this procedure costs approximately £7,000 and the equipment costs have therefore been included in the costing exercise.

Table 6-17: The average cost per patient implanted with a thalamic DBS

	Assess ment	Intervention		Follow-up				TOTAL
		Equip £	LOS £	Rehab £	Follow Up £	PT visits £	Radio £	£
1 (♣)	211.37	7,000	4,602	1,783.18	295	266	20	14,177.55
2 (♣)	211.37	7,000	4,602 + 9 days	1,783.18	295	95	20	14,006.55
3 (♣)	211.37	7,000	4,602	891.59	295	54	20	13,076.96
4 (♣)	211.37	7,000	4,602 + 12 days	8,661.16	295	38	20	20,827.53
5 (♣)	211.37	7,000	4,602 + 3 days	5,476.91	295	54	20	17,719.28
6 (♣)	211.37	7,000	4,602 + 14 days	3,184.25	295	38	20	15,350.62
7 (♦)	211.37	715	2,697 + 2 days	32,224.61	73.50	-	-	37,826.48
8 (♣)	211.37	7,000	4,602 + 34 days	13,119.11	295	38	20	25,285.48
9 (♣)	211.37	7,000	4,602 + 4 days	-	295	38	20	12,166.37
10 (♣)	211.37	7,000	4,602 + 5 days	1,273.70	295	95	20	13,497.07
11 (♦)	211.37	715	2,697 + 3 days	-	73.50	-	-	5,601.87
12 (♣)	211.37	7,000	4,602 + 5 days	-	73.50	-	20	11,906.87
13 (#)	211.37	-	1,982	-	295	-	-	2,488.37
14 (#)	211.37	-	1,982	-	295	-	-	2,488.37
15 (#)	211.37	-	1.982	636.85	295	-	-	3,125.22
Total Cost (excluding the assessment costs of those not proceeding to operation)								£209,544.59
Assessment costs of patients not proceeding to operation (22 x £211.37)								£4,650.14
Total cost (including the assessment costs for those not proceeding to operation)								£214,194.73
Average cost per patient of implantation with a thalamic DBS								**£14,279.65**

Legend: ♣= patients in whom thalamic DBS system was implanted, ♦ = patients in whom a DBS electrode only was implanted and # = unsuccessful attempts, Equip = cost of equipment, LOS = cost of length of stay, Rehab = cost of rehabiliatation, Follow-up = cost of follow-up assessments, PT visit = cost of physiotherapist's visits to reprogramme the DBS, Radio = cost of the transistor radio given to patients to confirm whether DBS was on or off.

6.7.6 Resource use (home care) after implantation

The majority of patients referred for thalamic DBS were severely disabled by the movement disorder and the MS and received assistance with ADL such as eating and drinking, either from a relative or from social services.

The amount of assistance required by patients at home with activities of daily living was estimated at the pre-operative assessment and then at the 12 month assessment by completing the self-care section of the Functional Independence Measure (FIM). As noted above, two primary outcome measures were used to detect change in the target upper limb at the four follow-up assessments: the MFTRS measured change in severity of tremor and the JTHF measured change in the performance of functional tasks.

There was a statistically significant improvement in both severity of tremor amplitude and functional performance of the Jebsen subtests in the target arm at all the follow-up assessments when the stimulator was switched on as reported earlier in the results. However this improvement did not have clinical relevance in that scores on the self-care section of the FIM did not show a significant change ($p= 0.67$, $N=9$).

There was no difference between the amount of assistance required by patients to carry out activities of daily living before the operation compared to 12 months after the operation. Consequently there was no reduction in the amount of help provided either by a relative or by homecare services after the thalamic DBS was implanted and therefore there was no saving on the cost of the homecare resources as patients. still required assistance with activities such as feeding, drinking and grooming.

CHAPTER 7

DISCUSSION AND CONCLUSION

7.1 Introduction

This chapter contains a discussion of the results of the study in terms of whether the purposes have been achieved and relevant hypotheses supported or rejected, and of issues that have emerged. The purpose of the study was first to devise and validate a standardized test for use with patients with MD due to MS and secondly to provide a preliminary evaluation of the relative merits and demerits of thalamic DBS and thalamotomy in management of patients with tremor due to MS. The emphasis was on measuring outcome in terms not only of quantitative change in tremor, but of changes in disability, handicap, aspects of quality of life and patient perception of effectiveness. The third aim of the study was to investigate the costs of thalamic DBS in relation to its benefits.

7.2 Methodological Difficulties

7.2.1 Ascertaining the clinical subtpe of MS

It was difficult to ascertain the clinical subtype of the majority of patients referred to this study (N = 37) either from the referral letter or the case notes where these were available. This was presumably because although the terms used to describe the form or clinical stage of the disease had been used for many years, there was no consensus among clinicians for the meaning of these terms before 1996 (Lublin and Reingold 1996). This classification is based on the evolution of MS-related impairment over time and many of the patients in the present study did not have regular contact with a neurologist so that the disease subtype had often not been determined.

Of the 15 patients who underwent thalamic DBS and were followed up over the course of the study 10 patients had entered the secondary progressive phase of MS having initially been diagnosed with relapsing-remitting disease. Secondary progressive MS tends to affect whichever system has borne the brunt of the disease earlier in the course and the cerebellar system is more frequently involved than in primary progressive MS (Matthews 1988).

In the present study the mean time after diagnosis of the disease to onset of the movement disorder was 7.8 years in the patients who underwent surgery (N = 15) suggesting that movement disorders were not the presenting feature of the disease. Five patients developed cerebellar signs early on in the course of the disease and had what appeared to be a more aggressive form of MS which could probably be

classified as progressive-relapsing MS. The disease was progressive from its onset in these patients, with clear acute relapses but continuing progression in the periods between relapses.

Despite the fact that the majority of patients who underwent surgery had secondary progressive MS and were therefore a particular subgroup of the MS population, there was wide variation with regard to the presentation of movement disorders within this group of patients. The group could be further subdivided into: patients in whom the MD predominately affected the upper limbs (16%); those in whom it predominately affected the axial muscles of the trunk and neck (3%); and those with movement disorders affecting both the axial and limb musculature (81%).

It appears that the patients referred for this study were at the severe end of the spectrum with regard to severity of disease and severity of movement disorder. Five patients were deemed not suitable for thalamic DBS because of severe associated neurological dysfunction and 6 patients were unsuitable because they presented with either predominant axial tremor or a combination of axial and upper limb tremor. In the latter sub-group thalamic DBS was unlikely to have a useful effect on the upper limb because of the severity of the movement disorder affecting the midline musculature.

In the present series, the most common presentation, in 30 (81%) of patients, was for the movement disorder to affect the upper limbs, head and trunk. A recent study by Alusi *et al* (Alusi et al. 1999b) assessed 100 patients in the MS Unit of the Central Middlesex Hospital and found that 57 exhibited tremor. There were major

differences between the patients in their study and those in the present study with respect of the presentation of movement disorders (See Table 7-1). They found that head tremor occurred in 7% and trunk tremor appeared in 5% of the patients and suggested that the movement disorders in these locations of the body were present in isolation as no mention was made of movement disorders affecting different areas of the body in combination. This seems unlikely given the findings of the present study in which 6 (16%) patients had movement disorders affecting the upper limbs only and none of the patients had a movement disorders affecting just the head: it always appeared in combination with tremor in the trunk. Also, a much higher proportion of patients had involvement of the head, upper limbs and trunk in the present study suggesting that they were more severely affected by the MDMS. This is perhaps not surprising since the patients were referred for specific intervention to treat their movement disorders.

***Table 7-1*: Comparison of the presenting movement disorders of patients in Alusi et al's study and the present study**

Area of the body affected by the movement disorder	**Present study N = 37**	**Alusi et al's study N = 57**
Arms	97% (unilateral in 17%)	55% (unilateral in 31%)
Head	86%	7%
Trunk	27%	5%
Legs	Not assessed	11%
Combination	81%	no data given

7.2.2 Recruitment problems

The numbers of patients referred to this study was small and this must be taken into account when considering the findings. Incidental sampling of patients was used to recruit patients consecutively as they were referred to the neurosurgeon. In the case of this study it was necessary to assess all available cases to achieve satisfactory numbers. However patients were only selected if they were appropriate candidates for thalamic DBS implantation.

Thirty seven patients were assessed in order to recruit 15 patients for surgery and out of this group only 10 patients had implantation of the full thalamic DBS system. Therefore thalamic DBS is only appropriate for a small number of patients with MDMS and explains why there were difficulties in recruiting large numbers of patients. A multi-centred study would have been necessary to perform a randomized control trial. However this would have been extremely difficult to co-ordinate and probably impractical. A UK register of strereotactic surgery for MDMS may help to further address the role of stereotactic surgery in these patients.

The patients who had implantation of the thalamic DBS system were to some extent their own controls in that the DBS could be turned off and on at each of the post-operative assessments. However when patients' DBS were turned off at the post-operative assessments their ratings of severity of tremor and their performance on the Jebsen subtests often did not return to their initial pre-operative baseline scores. This was due to a beneficial microthalamotomy effect resulting from the operation.

Another difficulty which limited recruitment of patients was the organization of the NHS in 1996. Extra contractual referrals (ECRs) were required from the referring Health Authority/Board for patients living outwith Lothian region to be treated by the Western General NHS Hospital Trust. The GPs and neurologists of such patients faced administrative difficulties in attempting to secure an ECR for the patient. This involved numerous phone calls to make arrangements and letters requesting authorization. There were frequently problems with agreement of funding for the operation and for transport to and from Edinburgh. Unfortunately the requirement for ECR in the NHS at the time the study began imposed many barriers and severely limited our ability to perform the study other than on a regional basis.

The study was therefore carried out in as practical a way as possible although certain constraints militated against an ideal study design. The selection of patients for inclusion in the study was however likely to be representative of the population of MS patients with movement disorders referred for thalamic DBS, to which the results would be applied.

7.2.3 Problems with measurement

7.2.3 (i) Confounding variables

Confounding variables are those factors other than the treatment variable (thalamic DBS) that can cause differences in the dependent variables (severity of tremor, performance of the Jebsen subtests and all other measures). The main confounding variables which were present in this study were:

Bias

In this study the effect of thalamic DBS was confounded by the patients' knowledge of the treatment they received. This threat to validity was not possible to avoid as patients could not be 'blind' to the fact that they had had a surgical procedure performed. The patients were also given an information sheet before the operation which may have led to expectation bias, and influenced the patients' responses to questions on the different subjective questionnaires which were used to measure outcome in the study.

The examiner was aware of the treatment the patients received, which may have caused expectation bias in examiner ratings. The assessment of tremor and upper limb function was performed in a single blind fashion since the examiner was unaware of the status of the DBS but it was not possible to 'blind' the patients as they experienced a 'kicking-in' effect when the DBS was switched on. Although I was blind to whether the DBS was switched on or off at the post-operative assessments, the patients were well-known to me and the nature of the setting of the DBS was therefore often apparent. One way to control for this bias would have been for another examiner to replicate all assessments. This was not practical because patients with MS are easily fatigued and it was necessary to carry out 2 assessments (one with the DBS on and one with the DBS off) at each post-operative visit. Obtained independent ratings of videotape recording of all assessments was not practical and would not have eliminated some possible influence of examiner bias. Many of the design limitations and potential sources of bias might have been expected to exaggerate the apparent effectiveness of thalamic DBS.

7.2.4 Limitations relating of the tests

7.2.4 (i) Limitations of tremor rating scale (MFTRS)

Measuring tremor clinically is difficult because tremors manifest themselves in different and often complex ways. Tremors have characteristic on/off triggers and natural fluctuations in amplitude and to a lesser extent frequency (Bain 1998). The amplitudes of physiological and pathological tremors exhibit significant diurnal fluctuations (Elble and Koller 1990) .

The characteristics of a tremor are influenced by a variety of factors including the experimental environment and the patient's physical, emotional and mental state as well as the tremor's natural cycles. In most clinical studies, tremor is evaluated for only a brief period of time, usually minutes. Thus the major problem in patient with MS is how to obtain a representative sample of a movement disorder that is rarely stable. Also there could be some practice effect on tests used to assess severity of tremor as a result of repeated testing but there is no direct way of measuring this without a control group. However practice effects would be unlikely to be differentially potent when the DBS was on compared with off at any given assessment.

Intermittent 'jumps'of the patient's hands were observed by 4 examiners rating severity of tremor in 12 patients with ET and 8 patients with 'dystonic' tremor (Bain et al.1993) and these frequent 'aperiodic' but sudden increases in tremor amplitude would be the events most likely to cause a patient to spill a cup of coffee or ruin a piece of writing.

Another problem of assessing patients with severe flailing movement disorders in the upper limbs like those seen in patients with MS is that patients are usually unwilling to allow their arms to thrash about for even a few seconds (Bain 1998). This problem introduces a significant subjective bias to the observation and measurement of such movement disorders.

Holmes (Holmes 1917) suggested that fatigue might play an important role in the genesis of cerebellar postural tremor. Cerebellar postural tremor of the extremities is often asymptomatic until the patient has maintained a steady posture for several seconds (Gilman 1981). This was considered when assessing postural tremor in patients with MS as the patients were asked to attempt to maintain the posture for 15 seconds. The possibility that fatigue could underlie cerebellar postural tremor has not been adequately investigated.

In 1917 Holmes (Holmes 1917) made detailed observations of patients with cerebellar injuries and he observed that simple actions which required movement at one joint only were fairly accurately performed, though complex movements were ataxic and irregular. Evidence of this was apparent in many of the patients in this study when they performed the finger nose test. They were often able to touch objects that they could reach with their fingers with their limbs fully extended more easily than when movements at the elbow or other joints were necessary. It may therefore have been advantageous to ask patients to touch the examiner's finger positioned at different distances in front of the patient – some close and some at the limit of the patient's reach.

The finger nose test was designed to quantify an accurate intentional movement and the kinetic/intention component of a movement disorder was measured by observing the patients move their index fingers towards a target (the examiner's finger). The examiner's finger is commonly placed at the limit of the patient's reach and therefore probably does not reveal the true extent of the kinetic/intention tremor resulting in the test having weak validity.

Holmes also noted that irregularity in direction and range was always more marked in rapid than in slow movements. In fact when the patients were asked to execute the movement slowly, or were urged not to hurry, there was little or no obvious disturbance (Holmes 1917). This observation may also have a bearing on the finger-nose test. There is no literature describing the methods for performance of the finger nose test or of the speed at which the test should be performed. This was a weakness of the present study and in hindsight it might have been beneficial to have asked the patient to perform the test at different speeds and then record the worst (highest) rating of kinetic/intention tremor.

Part C of MFTRS included questions about ADL which were confusing for both the examiner and the patient. The questions were concerned with unilateral and bilateral upper limb activities and did not specify which hand was being assessed. Therefore the patients who had no involvement (3% of patients) or unilateral upper limb involvement only (17% of patients) fared better than the patients with bilateral upper limb involvement (80% of patients) as they were still able to perform the tasks with the unaffected hand. The majority of patients had both upper limbs affected by the movement disorder and it might therefore have been better to omit this section of the

MFTRS especially as the self-care section of the FIM provided a detailed assessment of upper limb function which was valid and reliable for the measurement of ADL in this group of patients (Granger et al.1990).

Patients and the examiner also had difficulty separating tremor-related disability from overall disability caused by the MS when making a judgement upon the severity of tremor-related disability. It is likely that severe disability resulting from progressive MS may have influenced the scores of tremor-related disability. Consequently because the subjective assessment scores of the examiner and the patients of overall tremor-related disability did not provide a valid measure of tremor related disability the results of the comparison at each evaluation should be regarded with caution.

7.2.4 (ii) Limitations of the EDSS

The Kurtzke Scales are the only widely used and recognized scales in multiple sclerosis research but they are impractical in clinical practice and very insensitive to changes in impairment and disability. The severity of tremor in a patient's target arm may improve but this will not be reflected in the Kurtzke cerebellar functional system as the scale does not allow for different areas of the body to be scored individually but provides an overall score of the severity of tremor. The type of tremor or location of the tremor are not considered. Thus it is a very crude measure of tremor severity.

The neurologist scored the cerebral functional system of the Kurtzke Scale at the pre-operative assessment and scores showed cognitive deficits in 40% of the patients

who subsequently underwent implantation of a thalamic DBS. Detailed neuropsychological assessment revealed that in these patients the mean initial test score (142, SD = 13 N = 15) was far below the level of comparable normal controls (168, SD = 4, N = 54). Only one patient who proceeded to implantation scored above the fifth centile level (score = 159) of normal controls.

The Kurtzke FS has poor validity for severity of tremor and cognitive function. Not surprisingly in relation to both its reliability and responsiveness the EDSS has been subject to considerable criticism (Noseworthy et al. 1990; Whitaker et al. 1995; Willoughby and Paty 1998) .

7.2.4 (iii) Limitations of tests of upper limb function (JTHF)

To perform a motor task with a limb a patient requires an adequate background of postural control and stability of the trunk and limb girdle so that the movement can be executed in a smooth and co-ordinated fashion. To reduce the truncal ataxia and achieve a degree of truncal stability the patients in the present study often had to be provided with a supported sitting position which necessitated reclining the back of the wheelchair slightly and in more severe cases providing some restraint by using a thoracic harness. This reclined position created a problem when patients attempted to use their upper limbs for function as the distance to a table in front of them was increased and the angle of the head limited their visual control of the task in question. Visual control is important in improving accuracy of movements (Jeannerod 1984; Prablanc et al. 1979) and the cerebellum plays a significant role in

co-ordinating all sensory inputs with motor activity to ensure smooth voluntary movements take place (Costeff et al. 1990).

Holmes (Holmes 1917) noted that disturbances of movement were not improved by vision and patients were as bad at performing movement with their eyes open as with their eyes closed. However it has been observed that in some patients with cerebellar tremor, removal of visual feedback improves movement (Findley 1988). Removal of visual feedback probably has an effect by influencing the abnormal dysmetric component occuring with the movement. Several patients in this study reported that it was easier for them to keep their heads still whilst being fed by others if they did not see the food coming towards them.

Difficulties arise in the measurement of upper limb function because it is a product of a multiplicity of factors, many of which are vaguely defined. The personality and motivation of patients will contribute to their willingness to perform the test. In addition the physical (eg. visual impairment, sensory abnormalities, fatigue) and mental state of the patient will also affect participation and may negatively influence the patient's performance.

Slowness, awkwardness and irregularity of finger movements were apparent when MS patients handled objects. The difficulties in bringing each finger of the affected hand separately and accurately to the tip of the thumb have been described in detail (Holmes 1917) . These disorders of movement became even more apparent when the patient attempted to use simple and familiar tools. For example, in writing the pencil was held incorrectly and insecurely, often grasped too tightly, and its point was

pressed much too firmly into the paper. The letters were frequently unequal in size and irregularly spaced: the individual letters were badly formed and their lines were often jerky and angular. As patients attempted to write they paused frequently, especially between the up-and down-strokes of the pen and the movement of the pen was consequently interrupted and discontinuous.

Another major influence on the patients' ability to perform the test may be the environment in which the test is performed. A test performed in a hospital environment may give a very different picture of the patients' ability from that in their home environment.

There are limitations to the inferences that can be made from the JTHF. Jebsen *et al* (Jebsen et al. 1969)chose activities that they thought to be representative of hand functions normally used in the performance of ADL. However, no correlation was observed by the authors between the performance of the tests and performance of a standardized upper extremity ADL test to test the validity of the subtests. Therefore the validity of the JTHF is questionable as the theoretical argument that supports the use of the JTHF for specifically measuring ADL was not proven.

Lack of evidence for validity and reliability is one of the principle problems in much of the research on assessments that are currently in use. However from the literature it is apparent that efforts are now being made to rectify this problem. The work of Jones (Jones 1986) was not considered until the JTHF had been chosen for use in the present study and it revealed that the JTHF is not a predictor of ADL but is predictive of change and is able to detect mild dysfunction in patients with tremor.

However the JTHF fulfilled most of the criteria which should be demonstrated by a scale which provides accurate assessment of function (Liang and Jette 1981) : it had been shown to give consistent scores when repeated in patients with neurological conditions and to give good agreement in scores when administered by different observers; data collection methods had been standardized; and it included a range of functional activities which were problematic to patients with MDMS.

Changes in the successful performance of subtests were of greatest importance in following the patients with MDMS in this study. If a patient was unable to pick up the kidney beans on the teaspoon before the operation but was able to accomplish the task after operation, it was concluded that there had been an improvement in performance on this task. Assessment of the total number of successful Jebsen subtests (out of a total of 7) with the DBS on and off, provided an estimate in change in performance in the subtests over the study period but it was not used to draw conclusions regarding function in ADL.

There are many different and complex movements involved in upper limb function and it is probably not possible to devise a test which incorporates them all.

The clinical assessment of the patients in this study with MDMS involving the upper limbs, trunk and head highlighted two important points. First upper extremity function cannot be thought of in isolation. In this group of patients although severe upper limb movement disorders were often the main reason for seeking help 81% of the patients had involvement of the head and trunk also. In some cases movement disorders affecting predominately the axial musculature greatly contributed to the

difficulties in using the upper limbs (shown in the video tape). Function of the hand is therefore not only dependent on the integrity of the shoulder and elbow but also on trunk stability to allow the appropriate positioning of the hand in space to complete the desired task. In upper motor neurone lesions a fully functioning hand is useless if the proximal function of being able to hold and place the limb is not present and *vice versa* one can have normal proximal stability which is useless if one does not have a functioning hand.

Secondly this study showed the importance of thinking of upper extremity function in the context of the patient's overall physical condition. All 15 patients who underwent thalamic exploration had other impairments due to MS besides cerebellar dysfunction. They all showed pyramidal or cognitive dysfunction. The brain stem, sensory and visual systems were affected in 87% of patients and bladder and bowel function was impaired in 73% of patients. The diffuse damage to the CNS resulted in a multiplicity of symptoms which contributed to overall disability and necessitated assistance from others in ADL.

As a consequence, improvement in performance of the Jebsen subtests did not increase independence in ADL in the majority of patients. The majority of patients still required the same level of assistance with ADL and home care resources. This study does not demonstrate that upper limb function was unimportant to these patients but it merely indicates that upper limb function must be placed in the context of the patient's total physical, mental and social status. There was an improvement in the number of successful Jebsen subtests passed after implantation of the thalamic

DBS. The study provides further evidence that the JTHF does show change over time in performance of the subtests but it does not predict performance of ADL.

The Assessment of Motor and Processing Skills (AMPS) has very recently been used to show that thalamic DBS in PD and ET patients resulted in a variable improvement in domestic tasks of daily living (Hariz et al. 1998). The AMPS consists of 56 standardized domestic tasks which vary in degree of difficulty. The patients choose to perform at least two different tasks with which they were familiar and usually performed in their daily life (eg. making a sandwich, hoovering, ironing a shirt). The AMPS might have been a suitable test to use in the present study in that its use has been extensively documented in the assessment of MS patients and reliability and validity have been reported to be satisfactory. In patients with tremor, the advantage of using the AMPS is that it clarifies whether the underlying impairment affects the patient's ability to perform routine domestic activities of daily living. However examiners require special training to learn to score the AMPS and its administration is time-consuming when used to assess both on and off states in Hariz's study the assessment lasted 80 – 100 minutes. Patients in the present study might not have been able to tolerate this lengthy assessment owing to the problem of fatigue which affects many patients with MS. It is important that evaluation of stereotactic surgery for tremor should include careful assessment of the patient's abilities in performing ADL but patients with MS may be more limited in this area by other impairments owing to the disease resulting in a greater disability than in patients with PD and ET. There would also have been a floor effect if the AMPS had been used in the present study as only two of the patients (patient 2 and 9) who underwent thalamic DBS

were able to participate in domestic tasks such as household management and preparation of meals after the operation.

7.2.4 (iv) Limitations upon the measurement of upper limb disability

The scales (self-care section of the FIM) and tests (JTHF) which measured the functional disability relating to tremor in the target arm were important in this study. The BI was used to provide an overall measurement of functional ability. This was important as in 2 patients the severity of tremor improved after operation but due to surgical complications (thalamic haematomas which occurred at the time of the operation) the patients were less independent 12 months after the operation compared with before. All other patients' Barthel Index scores were either the same or better 12 months after operation. This deterioration in general functional ability was not evident from scores on the self-care section of the FIM but it was from scores on the BI. The mean and median FIM scores were slightly higher 12 months after the operation (mean = 24, median = 24) than before the operation (mean = 23, median = 24) indicating that there was little or no reduction in the amount of assistance required by patients to perform the activities included in the self-care section of the FIM. Barthel Index scores were lower (mean = 9, median = 7) 12 months after operation than before operation (mean = 10, median = 13) indicating that the patients general level of ability in performing ADL had if anything decreased.

The ability to feed oneself more easily was the item that showed most improvement when the 12 month assessment was compared with the pre-operative assessment using the FIM (7 patients improved, N = 9) and the BI (3 patients improved, N = 9).

7.2.4 (v) Limitations of self-report scales

Although it is important to obtain subjective evaluations by the patients about their perception of the outcome of any intervention or treatment it is important to be aware that patients with MS often have cognitive deficits which may affect their memory and their insight into their problems. A significant correlation was found between poorer mental functioning and longer duration of MS ($\rho = -0.61$, $p = 0.01$, $N = 20$). This is not surprising as it is now recognized that cognitive dysfunction is a common symptom in MS (Beatty 1993; Rao 1986). The extent of neuropsychological impairment shown by most of the patients in this study was likely to invalidate self report estimates of change as a result of surgery and perhaps self report estimates of tremor related disability.

At every evaluation the tremor related disability as rated by the patient and compared to that of the examiner differed: patients' ratings of their disabilities tended to be less severe than the examiner's ratings. Radatz et al's study (Radatz et al. 2000) which looked at the functional outcome after unilateral and bilateral pallidotomy for Parkinson's disease also highlighted this discrepancy: patients described greater postoperative functional gains than the people who looked after them on equivalent questionnaire measures of outcome.

Most of the patients in the study required assistance to fill out the questionnaires because of their inability to write. This is a potential source of bias and it should therefore have been quantified by asking the additional question 'Did anyone help you to complete this questionnaire and if so who?'

7.3 Problems Associated with the Use of Thalamic DBS

7.3.1 Operative problems

Accuracy is paramount for the safety and efficacy of thalamic DBS. Localization techniques vary from one centre to another, and include microelectrode recording and CT/MRI guided stereotaxy and image fusion techniques using functional maps of the brain (Goldman and Kelly 1995). In this study CT imaging was used to estimate the target site in the ventrolateral nuclear complex after consideration of the pre-operative MRI. Adjustments were made after intra-operative stimulation. However stimulation at the predicted co-ordinate location for the ventrolateral nucleus of the thalamus did not always elicit the expected response. In many of the patients the neurophysiological responses usually elicited during stereotactic thalamo-capsular stimulation or improvement in the movement disorder were absent despite preserved contralateral limb function. The responses to rostral midbrain stimulation (induced eye movements and pupillary changes) were however preserved. Under these circumstances the surgeon elected not to insert an electrode purely by anatomical localization.

In a series of thalamotomies involving 9 MS patients (Whittle and Haddow 1995) similar difficulties with locating the target were reported and may be related to the focal and diffuse cerebral atrophy caused by MS. A common finding at autopsy is the significant percentage of patients with MS exhibiting enlargement of the ventricular spaces (Brownell and Hughes 1962). Brownell and Hughes have suggested that ventricular dilatation may be a compensatory change due to loss of peri-ventricular

white matter. Interestingly the results of the Whittle/Haddow study were almost identical to a thalamotomy series using CT/MRI image fusion techniques (Aziz 2000) in terms of immediate outcome, complications and impact on the movement disorder.

7.3.2. Complications resulting from operation

Complications associated with stereotactic surgery can result in transient deficits which are probably related to focal trauma caused by insertion of the stereotactic probe (Tomlinson et al. 1991). Permanent deficits can also occur and are due to inaccurately placed lesions or ablative lesions that are too large. Any gains achieved by thalamic DBS must therefore be weighed against both predictable and unanticipated risks of the surgery to the individual patient. In respect of complications occurring either during or after the procedure, the risks remain unclear as results in the literature are often ill-defined. For example, many post-operative deficits are reported as being transient but adequate description of the gradient or extent of recovery is characteristically lacking and indeed may be impossible in a progressive degenerative disease such as MS. Furthermore, a clear distinction is generally not made between intra-operative complications (eg. haemorrage) that may or may not have long term sequelae and post-operative complications (eg. seizure, dysphasia) that may be associated with a well placed lesion and an otherwise good neurological outcome.

7.3.2 (i) Haemorrahge

There is the question of whether multiple passes associated with intra-operative stimulation to locate a suitable target may increase the risk of complications. However the potential risk of haemorrage from multiple probe passes must be balanced against the risk of injury to the vital structures which surround the ventrolateral nucleus of the thalamus. An inaccurately placed DBS electrode may lead to long term adverse consequences for the patient.

The mean number of tracks made during stage one of the procedure in which a successful thalamic target was located was 5 (range 1 – 11, N = 15). The notion that a greater number of tracks might be associated with increased morbidity was found not to be the case. The patients in whom haemorrhagic complications occurred (patients 7, 8 and 15) had 3, 3 and 11 passes of the DBS electrode respectively. Patient 4 who had 6 passes of the DBS electrode, had transient limb weakness which recovered fully to pre-operative levels after rehabilitation (as assessed using the Barthel Index). CT scans were performed to confirm or exclude the presence of haematomas in the patients. However patients 7 and 8, who both had only 3 passes, were left with minor residual motor deficits in the target upper limb and lower limb at 12 months, and paradoxically a reduction in their movement disorders. The small haemorrhages which occurred in these patients probably began during electrode placement but the associated deterioration in clinical condition was not apparent until after the operation (1 hour and 24 hours post-operatively). Experience with DBS in Parkinson's disease and ET has revealed a very low rate of intracerebral complications (Benabid et al. 1991). Benabid *et al's* study, which also included 4

patients with MS, described one MS patient with a small haemorrhage around the tip of the electrode, noted 10 days after implantation. The patient developed a mild aphasia and slight right hemiplegia which supposedly improved within 2 months although no information was provided to clarify to what extent the improvement took place.

Geny *et al*'s study (Geny 1996) of thalamic DBS was performed on 13 patients with MS. The general status of the patients and severity of MS pre-operatively was not defined. Similarly Schuurman et al (Schuurman et al. 2000) claimed that thalamic DBS is safe despite the fact that one of the patients in the study, a man with Parkinson's disease, died after suffering an intracerebral haematoma. The results of the present study showed that 3 of the 15 patients (20%) who underwent thalamic exploration suffered thalamic haematomas, of whom 2 had long-term adverse sequelae which resulted in reduced independence in ADL. This may be a slight underestimate of the risk of haemorrage as another patient (patient 5) presented with transient lower limb weakness after the operation although a haematoma could not be identified by MRI scan.

The chance of haemorrhage occurring as a result of the operation was discussed with the patients pre-operatively and the risk of this happening was given as 1% if the patient was under the age of 40 and 5% if the patient had high blood pressure or was older. These estimates were based on the studies carried out by Benabid and others (Benabid et al. 1991; Benabid et al. 1996a) and were an underestimate of the risk of haemorrhage in patients with MS undergoing similar surgery.

It would therefore seem that there is greater risk of haemorrhagic complications associated with thalamic DBS in patients with MS than either Parkinson's disease or ET. Certainly the side effects of thalamotomy in patients with MS are known to be more severe than those observed in PD and ET. In their series of 11 patients Speelman et al (Speelman and Van Manen 1984) reported permanent hemiparesis in four cases in their series of 11 patients, and one died of an aspiration pneumonia 3 weeks after surgery; Barnett et al (Barnett et al. 1992) observed permanent hemiparesis in two out of six thalamotomy patients. Also there was concern that stereotactic thalamotomy might provoke relapse in multiple sclerosis patients (Speelman and Van Manen 1984) and relapses have been reported after implantation of thalamic DBS (Geny et al. 1996) but the association between thalamic DBS and resulting deterioration is difficult to establish because of the progressive nature of the disease.

The findings of this study therefore show that there can be significant procedural morbidity associated with DBS insertion in patients with MS with advanced disease (Goldman and Kelly 1995).

7.3.2 (ii) Infection

One patient in the study (patient 4) developed a staphlococcus aureus infection in the IPG site one month after the IPG was implanted. Aspiration of the collection and antibiotic therapy (oral and intra-venous) was given and the infection seen to resolve. However owing to reactivation of the infection around both the IPG and the

extension lead they were both removed 11 months after operation. The DBS electrode was left *in situ*

Equipment-related complications have occurred in 2 studies which included patients with MS in their cohorts but the patients who suffered complications were not identified by their diagnoses in either study. Benabid *et al*'s series of 117 patients (Benabid et al. 1996) (of whom 4 were patients with MS) reported local skin problems in 5 patients: 3 had late scalp infections and erosion necessitating removal of the DBS electrode and connector; 2 patients had a granuloma along the connector extension wire track and one patient had a transient fluid collection in the subclavicular pouch of the IPG. In the other more recent study of 34 patients who underwent thalamic DBS, 5 patients with MS were included and there were two equipment related complications (Schuurman et al. 2000). In one patient the pulse generator site became infected and the IPG needed to be replaced after antibiotic therapy, and one patient had a haematoma near the pulse generator.

7.3.2 (iii) Seizures

Two of the patients suffered solitary seizures after the operation but it is not clear whether they were related to the to the thalamic DBS. Neither patient had seizures pre-operatively. One patient had a grand mal seizure one week after the IPG was implanted and another 8 weeks after implantation. At the time of the seizures, the stimulation voltages were 3.3V and 3.8V respectively.

7.3.2 (iv) Mood disturbance

Mood disturbances occurred in 5 patients after surgery either because the operation was unsuccessful (a target could not be located that suppressed tremor) or the result was not considered to be the expected outcome. This occurred despite the fact that the research team adopted an extremely cautious approach to this therapy and often the main but rather limited objective was to restore minimum use of the upper limb. The patients were informed at length of what might be expected from the operation and the risks involved. Unrealistic expectations in patients with MS have been reported in association with thalamotomy in the past (Speelman and Van Manen 1984).

7.3.3 Microthalamotomy effect

A microthalamotomy effect due to lead implantation, which results in immediate suppression of tremor is a well documented effect of thalamotomy and thalamic DBS (Pollack et al. 1993). Benabid reports that this effect is responsible for 'a transitory tremor suppression for a few days' (Benabid et al. 1993). As this effect wanes, the parameters of stimulation must be adjusted and Pollack *et al* reported that the stimulation intensity necessary to alleviate tremor, increased after implantation, reaching a plateau after approximately 6 weeks, and then remained steady in the majority of patients. In a recent study of thalamic DBS in patients with Parkinson's disease and ET the researchers waited for 1 year to elapse after surgery before assessing patients assuming that the eventual microthalamotomy due to implantion of the electrode would have vanished (Hariz et al. 1998).

The speed at which the microthalamotomy effect wanes would therefore appear to be debatable. Also the extent to which the effect can be said to have worn off is also not clear in any of the papers and the beneficial effect on severity of tremor has not been measured objectively. To assess the effect of thalamic DBS with confidence, the microthalamotomy effect should have disappeared completely thus tremor should be present at the pre-operative severity when assessed with the DBS switched off.

This was not possible in the present study as waning of the microthalamotomy effect did not occur completely and was still present to a varying extent in 10 of the 15 patients assessed 12 months after operation. The extent of the microthalamotomy effect on severity of tremor and performance of the Jebsen subtests can be seen in the individual patient graphs (section 6.5 Figures 6.5 – 6.19).

In patients 7 and 11 the beneficial microthalamotomy effect was so pronounced immediately after the operation that the patients did not proceed to implantation of the IPG and in 7 other patients (who did proceed to implantation of a thalamic DBS) a beneficial microthalamotomy effects was still evident at the one month post-operative assessment when assessment involved either or both of the primary outcome measures (shown on either the tremor figure or the Jebsen figure for each individual patient in Section 6.5). Three patients in the present study did not proceed to implantation of the IPG but showed persisting microthalamotomy effects after surgery: 1 patient after thalamic exploration (patient 15) and 2 patients after implantation of thalamic electrodes (patient 7 and patient 11).

It is possible that the improvements reported in previous studies of thalamic DBS in patients with MS may have been related to microthalamotomy rather than to functional inactivation of the presumed thalamic pacemaker by thalamic DBS (Benabid et al. 1996b; Brice and McLellan 1980; Geny et al. 1996b; Nguyen and Degos 1993; Schuurman et al. 2000; Siegfried 1993). None of these studies presented data to enable a comparison to be made between the effect produced when the DBS was on compared with the effect when the DBS was off at the post-operative evaluations. Therefore it is not possible to deduce whether improvement reported in the outcome measures was due to the effect of the DBS or to the effect of microthalamotomy. Claims that the improvement was due to thalamic DBS can therefore not be accepted with confidence from these studies. Benabid *et al* (Benabid et al. 1991) reported a patient with MS in their series who presented with a small haemorrhage around the tip of the electrode 10 days after implantation of a thalamic DBS. At the time of the haemorrhage the tremor was totally controlled by stimulation and disappeared even when the stimulation was turned off and never recurred. It therefore seems plausible that this excellent outcome in terms of suppression of tremor may in fact have been due to a microthalamotomy effect rather than the stimulation effect.

The present study was the first study to evaluate the effect of thalamic DBS by presenting data that compares tremor severity with the DBS on and DBS off at each of the post-operative assessments with the pre-operative score of severity of tremor. By doing this the study allowed the extent of the microthalamotomy effect of the operation to be objectively measured at each of the post-operative assessments. The

findings of the present study suggest that the beneficial persisting microthalamotomy effect has probably been under estimated in previous studies.

It also raised the question of whether the microthalamotomy effect associated with the surgical procedure of implanting a thalamic DBS electrode was the same as the microthalamotomy effect associated with the ablative procedure used in thalamotomy. This is an important question and it is likely that the effects are not identical. The effect that results after thalamotomy appears to wane as studies demonstrate that patients show reoccurrence of tremor at 12 months (Aziz 2000; Haddow et al. 1997; Hooper and Whittle 1998) after thalamotomy. Ten patients in this series however still showed a beneficial effect 12 months after operation when the DBS was off which can only be due to the placement of the electrode within the thalamus.

Thalamotomy produces a lesion at a specific site of the thalamus. This accounts for the marked improvement in tremor suppression immediately after thalamotomy which wanes with time as the dysfunctional volume contracts. However in DBS the electrode is left in situ and this may account for the seemingly permanent beneficial effect when the DBS is off coupled with an added beneficial effect when it is switched on. This is demonstrated on the video tape of the second patient showing the effect of thalamic DBS 12 months after operation, performing the volumetric tests with the DBS off and then on.

The presence of a microthalamotomy effect would also explain why the effect of thalamic DBS seemed to be more pronounced immediately after the operation but

then appeared to be less effective with time. Most patients in this study required adjustment of the stimulation parameters in the first 6 months after operation owing to a reported reduction in the benefit of the DBS. However despite lengthy sessions aimed at readjustment of the parameters of stimulation it was not often possible to repeat the initial post-operative result and a sub-optimal result had to be accepted.

7.3.4 Need for rehabilitation and training

None of the studies reporting the effect of thalamic DBS for MDMS discussed any clinical problems that arose in the immediate post-operative period. However problems with post-operative recovery were encountered in this cohort of patients. Many patients in the post-operative period and were generally more fatigued and slow to return to their pre-operative levels of mobility. This resulted in an average length of stay in DCN for the 2 stages of the operation to be carried out of 15 days. The length of stay in hospital for implantation of a thalamic DBS and the post-operative recovery time of patients with MS have not been reported in previous studies. Shorter LOS (1 week) have been reported for the procedure when performed in patients with Parkinson's disease and essential tremor but the study implied that stages 1 and 2, of implanting the thalamic DBS electrode and the IPG respectively, were performed at the same operation(Hariz et al. 1998.

A comprehensive, integrated, multidisciplinary rehabilitation programme was required to support thalamic DBS insertion since some patients required general rehabilitation to return to their pre-operative level of functional ability; the stimulators needed programme adjustments; and some patients needed intensive

physiotherapy and occupational therapy to relearn use of the target limb. The average length of stay for the 9 patients who had a period of rehabilitation was 54 days. Three patients had exceptionally long stays owing to the development of post-operative haemorrhages resulting in transient (patients 5 and 15) and permanent (patients 7 and 8) reduced functional ability. The time spent in the rehabilitation units was reflected by the total cost of the LOS for rehabilitation for each patient shown in Table 6-17 and was considerable in the cases of patients 5, 7 and 8. No study of DBS for patients with MDMS has to date highlighted this requirement for rehabilitation post-operatively although it has been argued that inevitably the degree of success of thalamic DBS will depend on case selection, surgical technique and postoperative physiotherapy, aimed at optimizing functional gain (Alusi et al. 1999a) .

7.4 Problems With its Use

7.4.1 Turning the stimulator on and off.

Turning the thalamic DBS on and off was not straightforward. It was important to be aware of how the IPG had been positioned by the surgeon in the pectoral pouch in the patient's chest. The IPG was rectangular in shape and the surgeon usually implanted it with the longer side positioned horizontally; the base of the hand-held magnet with which the patient was taught to 'swipe' the IPG was also rectangular in shape and it was essential that the long side of the magnet was placed over the long side of the IPG to successfully switch the stimulator on and off. There were difficulties switching the IPG in one patient and this was because the IPG had been

implanted vertically and the researcher was not aware of this and therefore did not teach the patient to hold the magnet vertically.

Patients who underwent operation at the beginning of the study reported being uncertain as to whether or not the DBS had been successfully switched on or off by applying the hand held magnet over the IPG. This was because they often had difficulties holding the magnet correctly to swipe the IPG owing to poor hand function and poor co-ordination. It was therefore necessary to issue all the patients with a small transistor radio with instructions of how to perform an AM radio test in order to determine the state of the DBS (Appendix 31). This involved tuning the radio to its lowest setting on the AM waveband (530 Hz) but not on to a station. The volume was adjusted until a static noise was heard. The patient was instructed to pass the radio over the skin covering the IPG and if the IPG was switched on a loud interference noise was emitted from the radio.

Only 3 of the 10 patients who had DBS implanted were able themselves successfully to switch the DBS on and off every day using the magnet. The people who cared for the other patients at home and were responsible for getting them out of bed and putting them back to bed at night therefore had to be taught how to perform this task. This necessitated the researcher visiting the patients at home once they had been discharged to instruct the appropriate person.

7.4.2 Setting the amplitude of the magnetic field in the IPG

Apart from the normally programmed amplitude setting (which was programmed into the IPG before the patients were discharged from hospital) the IPG also had a

magnet setting. The research team were not aware at the beginning of the study that it was possible for the patient to switch the amplitude from one setting to another by holding the magnet over the IPG for longer than 6 seconds. Patients were taught to switch the DBS on and off by holding the magnet over the IPG for 2 seconds. However, because of the difficulties the patients had in holding the magnet correctly, they often inadvertently held the magnet over the IPG for too long. This caused a problem with 2 patients before this feature of the IPG became known. The patients accidentally switched to the magnet setting, which had not been programmed by the researcher and therefore was not set to deliver a current. The patients both contacted the researcher because the transistor radio was not emitting a buzzing noise when the DBS was switched on and they therefore assumed that the IPG battery was depleted and required replacement.

It was important that the magnetic field amplitude was set to be the same as the normally programmed amplitude so that if the patient did accidentally switch the IPG onto this mode it would deliver the same amplitude of stimulation. The researcher also had to remember to update and change the amplitude of the magnetic field if any alterations were made to the programming of the DBS at any stage.

7.4.3 Adjustment to the stimulator

During the course of this study readjustment of stimulator settings was undertaken in the majority of patients. In most instances settings were altered to regain the degree of benefit initially achieved particularly if the patient had experienced a microthalamotomy effect which tended to wane in the first month after surgery, or to

try to obtain a better effect. Some patients required many visits to achieve optimum tremor suppression as time progressed. This was both time consuming and costly. The mean number of visits for reprogramming was 4 (range 0 – 13).

This waning efficiency of the thalamic DBS was most often seen in the first month after surgery. This phenomenon has been reported by others (Benabid et al. 1991; Blond et al. 1992; Hubble et al. 1996) and may be due to loss of microthalamotomy effects post-operatively or to changes in impedence in the tissues associated with tissue injury and healing related to the procedure.

Adjustment to the parameters of stimulation was required initially in the post-operative period and was a common need in the first 3 months after operation. Thereafter most patients reached a stable situation or it was felt that the optimum tremor suppression had been achieved. Sometimes the effect was clinically disappointing despite extensive attempts at reprogramming the DBS. In some patients there was a need for a late increase in the amplitude of stimulation which may have been due to either the progression of MS or the development of escape or tolerance phenomenon. In these patients DBS became less effective with time and an increasing amplitude of stimulation was required to alleviate tremor. However a final level was reached as the stimulation amplitude could no longer be increased owing to adverse effects such as dysphasia and diplopia.

Tolerance has been reported by several authors (Benabid et al. 1996; Pollack et al. 1993) and could be due to a decreased biological response (habituation) of the neuronal network which results in brain accommodation to the stimulation. Pollack

reports that in his opinion tolerance phenomena occur more often in patients who require relatively high amplitudes of stimulation immediately after operation. This may occur in a patient with a sub-optimal electrode position in the ventolateral nucleus of the thalamus. The general understanding of tolerance phenomena has resulted in the strong recommendation to switch the stimulator off when not really needed, for example during sleep, and patients in the present study were advised to do this. Doing so will increase the battery life of the stimulator by 30% if the patient has 8 hours of sleep per day.

7.4.4 Parameters for stimulation with the IPG

Using an external computer it was possible to modify the parameters of stimulation and to test the efficacy of stimulation at each electrode contact in the thalamus. The parameters were set on discharge from hospital and the stimulation was often adjusted when the patients were evaluated at the 1, 3 6 and 12 month post-operative assessments. Each session of adjustment lasted approximately an hour. The intensity of stimulation was slowly increased until the patient complained of unpleasant transient dysaesthesia or dysarthria or hand and face dystonia with stimulation. If the tremor had not improved, another combination of electrodes was used or a change was made to the frequency and/or pulse width of the stimulation.

There was a wide variation in the parameters for stimulation of the IPG both when the patients were discharged from hospital after the implantation of the thalamic DBS and 12 months after the operation. The mean amplitude, frequency and pulse width which were clinically effective on discharge from hospital and at 12 months

were 2.7V (range 1.8 – 2.9V), 120Hz (range 30 – 185Hz), 120μs (range 60 – 160μs) and 3V (range 2.2 – 5V), 160Hz (range 130 – 185Hz), 110μs (range 60 – 150μs) respectively. It appears therefore that some patients responded to low frequency stimulation and others to high frequency stimulation in the early stages after operation. This contrasts with the finding that DBS suppresses tremor only when the frequency of stimulation is at least 100Hz (Benabid et al. 1996). The mechanism of action of DBS is still unknown but it could be due to the alteration of a transcortical reflex loop passing through the ventrolateral nucleus of the thalamus, in the same manner as thalamotomy. Instead of the removal by thalamotomy of a central oscillatory mechanism, electrical stimulation could inhibit this neuronal rhythmic firing, at least if the stimulating frequency reaches a level of more than 100 Hz (Benabid et al. 1991). If this hypothesis is accepted, low frequency stimulation used in some of the patients in this study post-operatively should not have had an effect.

At 12 months the range in the frequencies (130 – 185 Hz) and pulse widths (60 – 150μs) of stimulation between patients were smaller than immediately after operation (30 – 185Hz, 60 – 160μs) although the range of stimulation amplitudes was larger (2.2V – 5V, 1.8 – 2.9V). This may have been because the researcher had become more proficient at programming the parameters for stimulation. The patients required higher amplitudes of stimulation at 12 months and in 8 of the 10 patients the optimum effect was achieved by assigning a positive polarity to the IPG casing and a negative polarity at the tip of the DBS electrode in the thalamus. The need for the late increase in stimulus amplitude may have been due to the progression of MS or the development of tolerance.

7.4.5 Rebound effect

In some cases when stimulation was turned off movements of the affected limb became very wild and in one patient (patient 2) were more severe than before the operation. These symptoms may be explained as rebound effects. Blond et al (Blond et al. 1992) reported that discontinuation of thalamic DBS can result in transient rebound tremor, a coarse tremor of greater intensity than the subject's baseline tremor. Objective evidence of this phenomenon is lacking and a study involving 10 patients with DBS implanted found that no rebound tremor was present when thalamic DBS was discontinued (Villagra et al. 1996). A recent study reporting the effects of thalamic DBS on PD's and ET allowed 30 – 45 minutes to pass after switching the stimulator off to avoid a rebound phenomenon (Hariz et al. 1998). This was not done in the present study as it was not a problem in the majority of the patients.

7.5 Findings of this Study

7.5.1 Reliability and validity contribution of MFTRS

FTRS was devised with a focus on the assessment of disorders of movement associated with Parkinson's disease and ET and it therefore required to be modified for use specifically with patients with MDMS. Once the necessary modifications had been made to the scale (MFTRS) there remained a need to examine the theoretical links between the objective measurement of the severity of the disorders of movement in patients referred for thalamic DBS and the MFTRS. A number of

studies were conducted to validate the measurement and reliability of the MFTRS in the assessment of patients with MDMS.

The first of these was to determine the reliability of a slightly modified Fahn's Tremor Rating Scale (MFTRS) when rating the severity of tremor in various parts of the body in patients with disorders of movement due to MS. All the examiners found the MFTRS simple to use when evaluating an edited video of the patients performing *ad hoc* tasks. In general, the results demonstrated good inter-examiner and very good examiner reliability although there were variations in examiner scores of tremor in different body regions. Assessment of tremor in the trunk showed a lower examiner and inter-examiner reliability although it still showed a satisfactory level of agreement. This difficulty in scoring truncal tremor may have arisen because there was less emphasis placed in the guidelines on how to assess tremor in the trunk than tremor in the upper limbs. This was because movement disorders involving the upper limbs were to be the main focus of attention for evaluating the effect of thalamic DBS. In contrast and more importantly, scores for tremor on the upper limb tasks showed good reliability. In particular, spirography provided a convenient standardized and consistently graded measure of the disability caused by a movement disorder.

The extent of examiner agreement in this study was a function not only of the inherent qualities of the assessment scale but also of features of the background and characteristics of the individual examiners. In this study the patients were assessed using a standardized assessment protocol, using a specified scoring procedure, under the same environmental conditions, with consistent directions. Differences in rating

levels found amongst examiners and suggests that in clinical or research studies it is advisable for either the same person or members of the same occupational group to perform the ratings of tremor.

As discussed previously it is difficult clinically to define the boundaries of action, intention and goal-related tremor, and to differentiate between these types of tremor and dysmetria (Bain et al. 1993). Because of these difficulties in clinical practice, it was decided that for the purposes of this study, kinetic and intention tremor should be assessed together by asking the patient to perform the finger/nose test, a test that is widely used for this purpose. Combining kinetic and intention tremor resulted in acceptable levels of examiner and inter-examiner reliability for the rating of kinetic/intention tremor. Goal-related tremor is tremor that occurs to any significant extent during the pursuing of a goal and in this study was assessed by observing the patient perform spirography, pouring and the subtests of the Jebsen Test of Hand Function – and was also found to have good reliability.

The second aspect of the study was to evaluate the validity of the MFTRS. Validity deals with whether or not a legitimate inference can be made from a scale of measurement or a test. To do this the scale is compared to a criterion. However this was not possible when measuring tremor as a 'gold standard' has not been defined. Aspects of validity of the MFTRS were assessed by calculating the correlation coefficients between the different component parts of the MFTRS and between them and measurements of impairment, disability and handicap, and the score on the Kurtzke scale for measurement of cerebellar function as scored by a neurologist. The pattern of correlation suggested adequate validity.

In conclusion, a composite of Fahn's TRS (MFTRS) provided a simple, concise, 24 item scale for evaluating movement disorders in MS. The measurement validity of the MFTRS was established and inter-examiner and examiner reliability scores obtained in this study using MFTRS show that it can be used with confidence in a clinical setting. However it should be noted that examiners should be familiar with the guidelines for using the scale and preferably should have experience in the field of clinical neurology. It is preferable for research purposes that one examiner performs the assessments.

7.5.2 Effect of thalamic DBS on impairment, disability, handicap and QOL

7.5.2 (i) Improved severity of tremor and its impact on ADL

Two previous studies, involving 26 patients with MDMS claimed that thalamic DBS was effective in approximately 70% of cases (Geny et al. 1996; Siegfried 1993). Geny's study reported that there was a significant reduction in upper extremity tremor when the patients had their forefingers near their noses: measuring what was referred to in the present study as postural b) tremor. Although Siegfried reported a similar level of success in his study, severity of tremor and function were not objectively quantified thus casting doubt on this claim.

In the present study, thalamic DBS reduced the severity of tremor amplitude of the target limb in all 12 patients who had either the thalamic DBS system or the thalamic DBS electrode implanted and the severity of tremor at all the postoperative assessments when the DBS was switched on was significantly less compared with the severity of tremor before operation.

Despite the statistically significant improvement in ratings of the severity of tremor and the scores for performance on the Jebsen subtests when the DBS was switched on, patients did not show a major functional improvement. Most of the patients had lost all use of the target upper limb preoperatively as a result of the severity of the movement disorder. The operation enabled them to grasp more easily grasp an object and manipulate it for simple tasks (eg. eating an apple) which was also a finding of Geny et al (Geny et al. 1996) ,but the patients still required assistance in most activities of daily living and there was no significant difference between scores on the self-care section of the FIM ($p = 0.67$) or the Barthel Index ($p = 0.67$) when the pre-operative scores were compared with the scores 12 months after implantation.

The severity of all types of tremor, particularly the postural components in the upper limb, was reduced. The severity of postural b) tremor improved the most in agreement with the findings of Geny *et al* (Geny et al. 1996). At the 6 month post-operative assessment 5 of 9 patients had no postural a) tremor (although 2 of these patients had no postural a) tremor pre-operatively either) and 4 of the 9 patients had no postural b) tremor. Kinetic/intention and goal-related tremor remained prominent and disabling as was observed in the studies by Narabashi (Narabayashi 1986) and Geny (Geny et al. 1996). In none of the 9 patients were these two types of tremor absent 6 months after the operation.

In other words, surgery had the effect of damping down the tremor generally and perhaps making life more tolerable for both the patients and their carers. Unfortunately this did not have a dramatic effect on enabling patients to perform activities of daily living with the target upper limb. Most patients had better postural

control of their heads and target upper limbs enabling them to be fed more easily by their carers and pick up and eat small pieces of food such as biscuits, sweets and pieces of fruit with the target upper limb. The persisting, although less severe presence of kinetic/intention tremor was disabling and prevented the patients from carrying out any skilled activities with the target upper limb such as feeding themselves with a utensil or drinking from a cup held in the hand. Patients still required the same amount of assistance with ADL from the people who looked after them whether friends and relatives or social services. This supports Benabid's view that:

> 'In MS the postural component of the tremor is usually well controlled but there is little effect on the action component and the cerebellar dysmetria.' (Benabid et al. 1993)

7.5.2 (ii) Patients' perception and handicap and QOL

Despite the fact that there was no significant change in the patients' ability to perform ADL as measured by the self-care section of the FIM and the Barthel Index, both the examiner and the patients perceived the patients' tremor related disability to be less severe after surgery than before (see Figure 6-20 in Chapter 6). At every assessment the patients' ratings of their tremor related disability tended to be marginally less than the examiner's ratings.

When patients in whom either an electrode or a thalamic DBS was implanted were asked about their opinions of the operation, most expressed some degree of satisfaction but 5 patients were dissatisfied with the outcome. Of these, 3 represented failures of the operative procedure and in the other 2, although implantation had been

carried out the procedure was discontinued. One of these had suffered a thalamic haematoma as a result of the operation.

Despite these findings there was no significant change in handicap as measured using the London Handicap Scale and the Handicap Questionnaire. The scores at 12 months after the operation indicated that patients perceived themselves to be more disadvantaged than before.

The aspects of QOL associated with MDMS that were studied showed little change. The only significant change noted was in the anxiety score of the Hospital Anxiety and Depression Scale. Patients perceived themselves to be less anxious 12 months after operation compared with before; however the number of people assessed at 12 months was small. Patients reported that they felt less embarrassed because the thalamic DBS had resulted in a beneficial cosmetic effect on the movement disorder and as the movement disorders were generally not as noticeable the patients felt more comfortable going out to public places with their friends and families.

There was no change in the fatigue experienced by patients despite the fact that it has been stated that in patients with MS with large amplitude movement disorders and complex tremor, reducing fatigue may be one of the objectives of thalamic DBS (Nguyen et al. 1996). Also almost all of the 13 patients in Geny's study claimed that the fatigue they experienced while performing some activities of daily living decreased owing to the relief of the tremor but this was not measured objectively (Geny et al. 1996) . Fatigue was however measured in the present study using the

FSS but a reduction of fatigue as a result of a reduction in the severity of the movement disorders was not experienced by patients.

In summary, thalamic DBS had an effect on impairment (severity of tremor) but it did not affect disability (ADL), handicap or aspects of QOL studied apart from perhaps reducing anxiety in the patients who underwent implantation.

A recent study (Rothwell 1998) has shown that patients with MS are less concerned than their clinicians about physical disability but more concerned with vitality and well being. Clinical trials evalauting stereotactic treatment for MDMS should therefore assess the effect of surgery on factors such as handicap and aspects of QOL which patients consider important.

7.5.3 Cost benefit of thalamic DBS

The assessment, intervention and follow-up costs of this novel treatment are considerable. The average cost per patient treated with thalamic DBS was around £14,000. This is more than the cost of treating patients with MS with interferon beta-1b for one year (£10,000 per year) (Swingler and Compston 1988). There were similarities between the results of the study on interferon-1b and the present study in that there was a high cost associated with the treatment which resulted in a modest clinical effects.

The £4602 given as the official cost of a stereotactic operation may be an under-estimate of the cost of thalamic DBS. This was because the average length of stay in the Western General Hospital was 15 days for these patients which is considerably longer than the average length of stay (7 days) of patients admitted for a typical

stereotactic operation such as brain biopsy. The figure used as a price for thalamic DBS did also not include any extra treatments or investigations such as drugs or CT scans required in connection with DBS implantation.

Thalamic DBS produced some improvement in patients' perception of their tremor-related disability but in this cohort of patients, because it did not achieve any substantial improvement in function in regard to performing activities of daily living with the target upper limb, it did not result in any economic benefits (savings in future care costs).

7.5.4 Clinical significance of the results

7.5.4 (i) Difficulty in predicting who will benefit

On clinical and neuroradiological grounds it is impossible to predict which patients may benefit from this treatment. Benabid observed that the efficacy of thalamic stimulation seemed to be limited when tremor was particularly violent during movement and when tremor was axial and predominated in the proximal parts of the limbs (Benabid et al. 1991). Seventy five percent of the patients referred to this study had axial tremor and had complex movement disorders with added ataxic and dysmetric components. Thalamic DBS was performed to treat the target arm but often the axial tremor continued to compromise the functional benefit on the stimulated side.

All the MRI scans showed diffuse hemispherical and brainstem plaques with distortion of the thalami and widening of the third ventricle. There was considerable

variation in the amount and locality of demyelination, plaques and brain tissue atrophy in both the pre-operative and post-operative images.

Not all patients referred and assessed were suitable candidates: 37 patients were assessed but of those only 10 went on to have a DBS implanted. If the patient's movement disorder predominately affected the upper limbs and the patient's target arm was potentially functional ie. had good strength, normal sensation and muscle tone he was regarded as being a good candidate. However if the patient had a movement disorder with severe axial involvement ie. titubation and/or truncal ataxia he was not regarded as good candidate. It was likely that such patients might require bilateral thalamic DBS to affect the midline musculature and it was impossible to assess their tremor during the operation as the head is fixed in the stereotactic frame.

Detailed pre-operative assessment was essential. Patients with MS may have a movement disorder but they may also have other symptoms such as weakness, reduced sensation, abnormal muscle tone which contribute to their movement disorders and may in fact be the main reason for the limitations of function. These patients were only likely to obtain a limited benefit from thalamic DBS. Nguyen (Nguyen et al. 1996b) argued that better selection with the exclusion of patients with severe associated neurological disorders should improve results.

Stereotactic treatment of tremor in patients with MS should probably be restricted to patients with stable disease whose tremor does not have a severe ataxic component and who have few other deficits (Schuurman et al. 2000). This is problematic in reality for several reasons. First, because of the nature of MS it is difficult to predict

the future course of a patient's disease. Patients with a stable relapsing remitting form of MS are probably the best candidates but 50% of patients who have relapsing remitting disease (70 % of patients with MS) will have converted to a secondary progressive form within 10 years (Weinshenker et al. 1997)

Secondly movement disorders do not commonly occur early in the course of the disease (Bauer 1978) and the early appearance of cerebellar ataxia indicates a poor prognosis (Matthews 1988). The mean duration of MS in this cohort was 13.3 years, and the mean duration of the onset of the MD from the time of diagnosis of MS was 7.8 years. Therefore, by the time the patients presented with cerebellar dysfunction and were referred for thalamic DBS, other neurological systems were affected. The patients were debilitated not only by the movement disorder but also by associated neurological dysfunction. This was reflected in the mean EDSS score of the patients which was 6.9 and indicated that they were severely disabled and dependent upon a wheelchair.

7.5.4 (ii) Progression of MS may mask improvement

> 'With MS patients there is a great difficulty isolating long term effects of the operation from changes due to the illness' (Haddow et al. 1997) .

Thalamic DBS is a palliative treatment for tremor. MS is a progressive disease and therefore patients are likely to deteriorate. The natural course of the MS may therefore mask improvement gained as a result of the intervention. Thalamic DBS did have an effect on the severity of tremor but it did not have an effect on the progression of the disease. Kurtzke EDSS scores were similar or worse at the 12 month assessment (mean = 7.3) compared with pre-operatively (mean = 7). The

scores of severity of tremor in the non-target arm were also compared to provide an impression of the progression of the MS. The findings showed that there was a slight progression in the disease over the course of the study in the patients who underwent implantation of a thalamic DBS. They were generally more disabled, more disadvantaged and had a reduced QOL 12 months after the operation.

7.5.4 (iii) Discrepancy between improvement in severity of tremor and performance of ADL

In this series thalamic DBS was found to be effective in reducing the severity of tremor and improving the performance of the Jebsen subtests. However these symptomatic and functional changes did not translate into a significant improvement in patients' performance in ADL or in patients' perceptions of overall gains in measurements of handicap and aspects of QOL. It was clear that a good result ie. improvement in severity of tremor and improved arm function measured by Jebsen subtests had often been achieved. However these symptomatic and functional changes did not translate into significant improvements in patient performance in ADL and therefore the benefits of the operation were clinically limited. The results of this study were therefore very relevant to future practice.

7.5.5 Consequences of continuing thalamic DBS for MS patients

7.5.5 (i) The benefit of thalamic DBS did not have significant impact on QOL/ADL

Despite the claims of previous studies that thalamic DBS is a safe procedure, the findings of this study suggested that there are considerable risks associated with implantation of a thalamic DBS in patients with MS. Permanent deficits due to

accurately placed lesions may result and the long-term effect on the risk of provoking MS relapses and accelerating the progression of the disease are still not known.

7.5.5 (ii) Are resources diverted from a more worthwhile use?

Thalamic DBS requires a considerable investment of time, personnel and resources. The procedure was not straight forward in the cohort of patients in the present study. Patients appeared to require longer stays in hospital to recover from the operation and in many cases needed rehabilitation and retraining of the target arm after implantation of the thalamic DBS. The costs of equipment were substantial and this needs maintaining at a cost since regular adjustment of the parameters of stimulation is necessary. Also at some stage the IPG battery must be replaced. There were therefore considerable foreseen and unforeseen costs associated with the implantation of a thalamic DBS. There was no reduction in resources (home care) after the thalamic DBS was implanted.

The health related QOL of people with MS is much lower than that of the normal population (Murphy et al. 1998) and age-matched controls of patients with other diseases (Holmes et al. 1998) and indeed other neurological illnesses (Vickrey et al. 1997). Therefore interventions which improve the QOL of people with secondary progressive MS more efficiently than thalamic DBS need to be identified. Continuing thalamic DBS for patients with MDMS will result in resources being diverted from more worthwhile use. It is possible that more benefit would be obtained from directing funds into supportive services (physiotherapy etc) for these patients as improvements in disability and handicap have been shown after in-patient

rehabilitation in patients with progressive MS (Freeman et al. 1996; Jones et al. 1996) .

7.5.5 (iii) Results of previous studies should be challenged

The results of previous studies of thalamic DBS for MDMS suggest improvement in approximately 70% of patients although these results are based on short follow-up time only 3 months after implantation (Geny et al. 1996; Siegfried 1993). Geny *et al* acknowledged that there was a discrepancy between the clear decrease of amplitude of the tremor and the poor improvement in ADL. The methods used in the present study enabled the microthalamotomy effect to be objectively measured for the first time and found that it was still present to a varying extent 12 months after the operation in 66% of the patients. This suggested that in previous studies there has probably been a gross underestimation of the influence of this effect on the final outcome and that the true effect of the thalamic stimulation was probably less than has been reported. Any future studies should be prospective and use comprehensive, multi-dimentional measurements for assessment.

7.6 CONCLUSIONS

The tremor of MS is often a component of ataxia which frequently affects the upper limbs, head and trunk. Ataxia and tremor commonly exist together and the movement disorder often includes dysmetria. The movement disorders rarely occur as isolated clinical signs and tend to present later in the course of the disease. The

progressive and cumulative neurological deficits in MS account for increasing disability, handicap and decline in QOL. For many patients with chronic incurable diseases such as MS the main objective of an intervention may be to lessen the effect of the disease by alleviating symptoms and maximizing the patient's ability to participate in activities by reducing disability and handicap. In the present study, the hypothesis that the treatment of disorders of movement in multiple sclerosis could be improved by the use of thalamic DBS was proposed; and prerequisite validation of a scale to assess such impairment was undertaken.

The work presented in this thesis had 3 main objectives. There was no validated scale available for the assessment of MDMS. Therefore the first objective of this thesis was to develop and validate a scale for measuring MDMS. The work carried out in this thesis proved the MFTRS to be reliable and valid for measuring MDMS. The potential use of the MFTRS is evidently great for both research purposes and for use in clinical practice, as no other validated scale exists for measuring MDMS. Despite the fact that there have been 7 studies that have reported outcome after thalamic DBS implantation in patients with MDMS since 1980, this study was the first study to use a tremor rating scale that had been validated specifically for use with patients with MDMS to measure the outcome of the intervention.

One of the recommendations of this study for future researchers would be that they should make a training video to assist in training examiners in the use of the MFTRS. Standardized assessment is essential to permit comparisons between examiners and between studies and this may be difficult to achieve if examiners are not familiar with patients with MDMS.The video could be similar to the video included in the

Appendix showing patients with varying severity of tremor and movement disorders affecting different areas of the body. It is anticipated that this would help the examiners to assess different patients with variable presentations of movement disorders.

The second objective of the study was to evaluate the long term effect of thalamic DBS on impairment, disability, handicap and aspects of QOL relevant to patients with MDMS undergoing implantation. Thalamic DBS significantly reduced the severity of the tremor (measured using the MFTRS) and it significantly improved performance of the target upper limb (measured using the JTHF) at 12 months compared to before the operation. However the benefits in ADL due to these symptomatic improvements in function were disappointing and unpredictable owing to persistence of cerebellar dysmetria, the coexistence of other associated neurological dysfunction that caused other disabling clinical features, post-operative complications and the progression of the MS. These findings are in agreement with those of previous studies although the follow-up time in the present study was considerably longer than in any of the other studies. The results of this study contrasted with those of previous studies by showing by showing that post-operative complications can compromise the beneficial effect of thalamic DBS.

Severe disability as found in this cohort of patients with MDMS (mean pre-operative EDSS score = 6.9) in whom thalamic DBS were implanted has been shown to be accompanied by decrease in QOL. Thalamic DBS resulted in a significant reduction in anxiety levels (measured using the anxiety section of the HAD) but did not have an effect on other aspects of QOL measured in this study.

The present study was the first study of thalamic DBS for MDMS which presented data comparing evaluations with the DBS on and off at every post-operative assessment. This showed that even when the DBS was switched off there was a beneficial effect on the ratings of severity of tremor and the successful performance of the Jebsen subtests when the scores were compared to the pre-operative (baseline) scores. Although this effect was only significant one month after the operation it was still evident in the majority of patients 12 months after the operation. 'Microthalamotomy' effect has been mentioned in previous studies but the magnitude and the length of time for which the effect persists has not been measured objectively. The results of this study suggest that the effect of microthalamotomy on outcome has probably been underestimated and the beneficial effect that has been attributed to the stimulation after implantation of a thalamic DBS may in fact be partly due to the persisting beneficial microthalamotomy effect. It is therefore very important that future studies should report data collected pre-operatively and data collected at the post-operative assessments with the stimulator on and off to determine if the reported benefit is due to the effect of the thalamic DBS, the microthalamomy effect or a combination of the two.

The third objective was to estimate the costs associated with thalamic DBS. In the NHS today there is increasing emphasis on evidence based practice. This study therefore attempted to address the issue of the outcome of thalamic DBS in relation to the cost of the intervention. The resources associated with the implantation of a thalamic DBS were substantial and arose from assessment; purchase (£7,602 per set) and implanting of the thalamic DBS; follow-up; comprehensive post-operative

rehabilitation requirement; staff costs for reprogramming the DBS and providing support. Results showed that a small benefit in terms of reduction of severity of tremor, improved performance on the Jebsen subtests and reduced anxiety after the operation was associated with high costs (approx £14,000 per patient implanted with a thalamic DBS). The beneficial psychological effect which was apparent in patients after the operation is probably far too modest to be considered cost effective for the NHS. However, to patients with severe disabling tremor in whom a cost saving intervention for MS is unlikely, they may not regard the improvement as 'modest'. If given a choice between the anxiety resulting from untreated tremor and thalamic DBS patients appear to be prepared to settle for small benefits which enhance this particular aspect of their quality of life.

It is probably appropriate to allocate more funds to people with MDMS but the resources used for thalamic DBS might have been better spent on identifying other more efficient ways of improving the QOL in patients with secondary progressive MS. Recent studies have shown interventions such as supportive and rehabilitation services (physiotherapy, occupational therapy) can significantly improve disability, handicap and QOL of people with MS and, realistically, far more benefit would be obtained from directing funds into these interventions. Also in view of the limited apparent benefit and high costs and risks of the procedure, it seems unlikely that a large controlled trial could be justified.

In conclusion the present study evaluated the effect of thalamic DBS on MDMD and in doing so highlighted important clinical, management and health implications associated with the operation and also some of the problems associated with its use

in this cohort of patients. The published paper in connection with the validation of the MFTRS has contributed to developments within the field of the assessment of MDMS. Evaluation of the complex movement disorders seen in patients with MS can now be performed with confidence in the clinical setting and treatments for disabling tremor in patients with MS can be properly evaluated.

BIBLIOGRAPHY

Agnew P, Maas F. (1982a) An interim Australian version of the Jebsen Test of Hand Function. *The Australian Journal of Physiotherapy*, 28: 23-29.

Agnew P, Maas F. (1982b) Hand function related to age and sex. *Archives of Physical Medicine and Rehabilitation*, 63: 269-271.

Aisen M, Holzer M, Rosen M, Dietz M, McDowell F. (1991) Glutethimide treatment of disabling action tremor in patients with multiple sclerosis and traumatic brain injury. *Archives of Neurolgy*, 48: 513-515.

Alusi SH, Glickman S, Aziz TZ, Bain PG. (1999) Tremor in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry* 66: 131-134.

Alusi SH, Glickman S, Worthington J, and Bain PG. (1999) A study of tremor in multiple sclerosis. *Journal of Neurolgy, Neurosurgery and Psychiatry* 66 (2), 264.

Amato MP, Fratiglioni L, Groppi C, Syracusa G, Amaducci L. (1988) Interrater reliability in assessing functional systems and disability on the Kurtzke scale in multiple sclerosis. *Archives of Neurology*, 45: 746-748.

Arsalo A, Hanninen A, Laitinen L. (1973) Functional neurosurgery in the treatment of multiple sclerosis. *Annals of Clinical Research*, 5: 74-79.

Ayres AJ (1963) Occupational therapy directed towards neuromuscular integration. In: Willard HS (Ed). *Occupational Therapy.* Philadelphia, J.B. Lippincott, 413-439.

Aziz T. (2000) Personal Communication

Bain PG, Findley LJ, Atchison P, Behari M, Vidailhet M, Gresty M, Rothwell JC, Thompson PD, Marsden CD. (1993) Assessing tremor severity. *Journal of Neurology, Neurosurgery and Psychiatry*, 56: 868-873.

Bain PG and Findley L. (1993) *Assessing tremor severity.* Smith Gordon Company Ltd.

Bain P, Findley LJ, ThompsonPD, Gresty MA, Rothwell JC, Harding AE, Marsden CD (1994) A study of hereditary essential tremor. *Brain*, 117: 805-824.

Bain P. (1995) Are neurophysiological techniques useful in differentiating tremor? In: Findley LJ, Koller WC (Eds). *Handbook of Tremor Disorders.* New York, Mercel Dekker, 79-93.

Bain PG. (1998) Clinical Measurement of Tremor. *Movement Disorders*, 13: 77-80.

Bain PG. (1999) A combined clinical and neurophysiological approach to the study of patients with tremor. *Journal of Neurology, Neurosurgery and Psychiatry*, 69: 839-844.

Barlow JS, Schwab RS. (1971) Mutual limb stabilisation in relation to tremor characteristics in Parkinsons and essential or heredofamilial tremor. *Neurology*, 21: 78-90.

Barnett GH, Kinkel RP, Bhasin C, Palmer J, Namey M, Rudick R. (1992) Stereotactic thalamotomy for intractable tremor in multiple sclerosis. *Neurology*, 42 (Supp 3): 327.

Bauer HJ. (1978) Problems of symptomatic therapy in multiple sclerosis. *Neurology*, 28: 8-20.

Baum HM, Rothschild BB. (1981) The incidence and prevalence of reported multiple sclerosis. *Annals of Neurology*, 10: 420-428.

Beals RK. (1966) Spastic paraplegia and diplegia: an evaluation of non-surgical and surgical factors influencing the prognosis for ambulation. *Journal of Bone and Joint Surgery*, 48A: 827-846.

Beatty WW, Goodkin DE. (1990) Screening for cognitive impairment in multiple sclerosis: an evaluation of the Mini-Mental State examination. *Archives of Neurology*, 47: 297-301.

Beatty WW. (1993) Cognitive and emotional disturbances in multiple sclerosis. *Clinical Neurology*, 11: 189-204.

Benabid AL, Pollak P, Gervason C, Hoffman D, Gao DM, Hommel M, Perret JE. (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet*, 337: 403-406.

Benabid AL, Pollak P, Seigneuret E, Hoffman D, gay E, Perret J. (1993) Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. *Acta Neurochir*, 58: 39-44.

Benabid AL, Pollack P, Gao D. (1996) Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *Journal of Neurosurgery*, 84: 203-214.

Beppu H, Suda M, Tanaka R. (1984) Analysis of cerebellar motor disorders by visually guided elbow tracking movement. *Brain*, 107: 787-809.

Blair VA. (1999) Hand Function. In: Durward BR, Baer GD, Rowe PJ (Eds). *Functional Human Movement.* Oxford, Butterworth Heineman, 59-179.

Blond S, Caparros-Lefebvre D, Parker F, Assaker R, Petit H, Guieu J-D. (1992) Control of tremor and involuntary movement disorders by chronic stereotactic

stimulation of the ventral intermediate thalamic nucleus. *Journal of Neurosurgery*, 77: 62-68.

Bond S, Thomas L. (1991) Issues in measuring outcomes of nursing. *Journal of Advanced Nursing*, 16: 1492-1502.

Bourdette DN, Prochazka AV, Mitchell W. (1993) Health care costs of veterans with multiple sclerosis: implications for the rehabilitation of MS. *Archives of Physical Medicine and Rehabilitation*, 74: 26-31.

Brice J, McLellan L. (1980) Suppression of intention tremor by contingent deep-brain stimulation. *Lancet*, 315: 1221-1222.

Brownell B, Hughes JF. (1962) The distribution of plaques in the cerebrum in multiple sclerosis. *Journal of Neurolgy, Neurosurgery and Psychiatry*, 25: 315-320.

Butler PB. (1998) A preliminary report on the effectiveness of trunk targeting in achieving independent sitting balance in children with cerebral palsy. *Clinical Rehabilitation*, 12: 281-293.

Carlson JD, Trombly CA. (1983) The effect of wrist immobilization on performance of the Jebsen hand function test. *American Journal of Occupational Therapy*, 37: 167-175.

Cella DF, Dineen K, Arnason B, Reder A, Webster KA, Karabatsos G. (1996). Validation of the functional assessment of multiple sclerosis QOL instrument. *Neurology*, 47: 129-39.

Cervera-Deval J, Morant-Guillen M, Fenollosa-Vasquez P, Vilchez-Padilla J, Burguera J. (1994) Social handicaps of multiple sclerosis and their relation to neurolological alterations. *Archives of Physical Medicine and Rehabilitation*, 75: 1223-1227.

Chase RA, Cullen JK Jr, Sullivan SA, Ommaya AK. (1965) Modification of intention tremor in man. *Nature*, 206: 485-487.

Chyatte S, Birdsong J. (1972) Methods-time measurement in assessment of motor performance. *Archives of Physical Medicine and Rehabilitation*, 53: 38-44.

Clifford DB. (1983) Tetrahydrocannabinol for tremor in multiple sclerosis. *Clinical Neurology*, 11: 189-204.

Collin C, Wade DT, Davis S, Horne V. (1998) The Barthel ADL index: a reliability study. *International Disability Studies*, 10: 61-63.

Compston A, Sadovnick A. (1992) Epidemiology and genetics of multiple sclerosis. *Current Opinion of Neurology and Neurosurgery*, 5: 175-181.

Compston A. (1986) The modern management of multiple sclerosis. *British Journal of Hospital Medicine*, 36: 200-208.

Costeff H, Groswasser Z, Goldstein R. (1990) Long term follow-up review of 31 children with severe closed head trauma. *Journal of Neurosurgery*, 73: 684-687.

Dean G. (1994) How many people in the world have multiple sclerosis? *Neuroepidemiology*, 13: 1-7.

De Castro P, Carreno M, Iriarte J. (1995) Types of fatigue in multiple sclerosis. *Journal of Neurology*, 242: 117-118.

Desrouleux R, Weinreb H. (1999) Fatigue in multiple sclerosis: Pilot trial of Selegiline. *Neurology*, 41: 321.

Deuschl G, Bain P, Brin M, Ad Hoc Scientific Committee. (1998) Consensus statement of the movement disorder society on tremor. *Movement Disorders*, 13: 2-23.

Ebers GC, Sadovnick AD. (1997) Epidemiology in multiple sclerosis. In:Paty DW, Ebers GC (Eds). *Multiple Sclerosis.* Philadelphia, FA Davis Company.

Ebrahim S. (1991) Measurement of impairment, disability and handicap. In:Hopkins, A, Costain, D (Eds). *Measuring the outcomes of medical care.* London, The Royal College of Physicians, 27-41.

editorial (1991) Recognising disability. *Lancet,* 338: 154-155.

Elble RJ, Koller WC. (1990) *Tremor,* London, John Hopkins University Press.

Fahn S, Elton R L. (1987) *Recent Developments in Parkinson's Disease,* New Jersey, MacMillan, 153-163.

Fahn S, Tolosa E, Marin C. (1988) Clinical rating scale for tremor. In:Jankovic J, Tolosa E. (Eds). *Parkinson's disease and Movement Disorders.* Baltimore-Munich, Urban and Schwarzenberg, 225-234.

Fallowfield L. (1990) *The Quality of Life: The Missing Measurement in Health Care,* London, Souvenir Press.

Feinstein A, Kartzounis LD, Miller DH, Youl B, Ron M. (1992) Clinically isolated lesions of the types seen in multiple sclerosis: a cognitive, psychic and MRI follow-up study. *Journal of Neurology, Neurosurgery and Psychiatry*, 55: 869-876.

Findley LJ, Gresty MA, Halmagyi G. (1981) A novel method of recording arm movements. A survey of common abnormalities. *Archives of Neurology*, 38: 38-42.

Findley LJ, Gresty MA. (1981) Tremor. *British Journal of Hospital Medicine*, 26: 16-32.

Findley L. (1988) Differential Diagnosis and Pharmacology. In: Jankovic J, Tolosa E (Eds). *Parkinson's Disease and Movement Disorders.* Munich, Baltimore. 243-257.

Findley LJ, Koller WC. (1995) *Handbook of Tremor Disorders,* New York, Marcel Dekker.

Folstein MF, Folstein SE, M^{c}Hugh PR. (1975) The mini-mental scale. *Journal of Psychiatric Research*, 12:189-198.

Freeman J, Langdon DW, Hobart JC, Thompson AJ. (1996) The impact of rehabilitation on disability and handicap in progressive MS: a randomised controlled trial. *Journal of Neurology*, 243: S17.

French S, Swain J. (1997) Changing disability research: participating and emancipatory research with disabled people. *Physiotherapy*, 83: 26-31.

Geny C, Nguyen JP, Pollin B, Feve A, Ricolfi F, Cesaro P, Degos JD. (1996) Improvement of severe postural cerebellar tremor in multiple sclerosis by chronic thalamic stimulation. *Movement Disorders*, 11: 489-494.

Geny C. (1996) Thalamic stimulation for severe action tremor after lesion of the superior cerebellar peduncle. *Journal of Neurology, Neurosurgery and Psychiatry*, 2: 234.

Gilman S. (1981) Cerebellar Hypotonia and Tremor. In:Gilman S, Bloedel JR, Lechtenberg R. (Eds). *Disorders of the Cerebellum.* Philadelphia, Contemporary Neurology Press, 159-173.

Glasby MA, Mallion RB. (1995) Physiochemical principles. In: Glasby MA, Huang, CL-H (Eds). *Applied Physiology for Surgery and Critical Care.* London, Butterworth, 3-14.

Goldman MS, Kelly PJ. (1992) Symptomatic and functional outcome of stereotactic ventralis lateralis thalamotomy for intention tremor. *Journal of Neurosurgery*, 77: 223-229.

Goldman M S, Kelly P J. (1995) The surgical treatment of tremor disorders. In:Findley, L J, Koller, W C (Eds). *Handbook of Tremor Disorders.* New York, Mercel Dekker, Incorporation, 521-562.

Goodkin DE, Hertsgaard D, Seminary J. (1988) Upper extremity function in multiple sclerosis: improving assessment sensitivity with box-and-block and nine-hole peg test. *Archives of Physical Medicine and Rehabilitation*, 69: 850-854.

Graham, J. (1999) What is MS? 2nd edition. London, Burnet Publications.

Granger CV, Hamilton BB, Keith RA. (1986) Advances in functional assessment for medical rehabilitation. *Topics in Geriatric Rehabilitation*, 1: 59-74.

Granger CV, Cotter AC, Hamilton BB, Fiedler RC, Hens MM. (1990) Functional assessment scales; a study of persons with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation*, 71: 870-874.

Haddow L, Mumford C, Whittle IR. (1997) Stereotactic treatment of tremor due to multiple sclerosis. *Neurosurgery Quarterly*, 7: 23-34.

Hallet MW, Lindsey J, Allelstein BD. (1985) Controlled trial of izoniazid therapy for severe postural cerebellar tremor in multiple sclerosis. *Neurology*, 32: 1374-1377

Hallet M. (1986) Differential Diagnosis of Tremor. In:Vinken, P J, Bruyen, G W, Klaeans, H L (Eds). *Handbook of Clinical Neurology.* Amsterdam, Elsevier, Vol. 49: 583-595.

Hamilton BB, Laughlin JA, Granger CV. (1994) Inter-rater agreement of the seven level Functional Independence Measure (FIM). *Scandinavian Journal of Rehabilitation*, 26: 115-119.

Hariz GM, Bergenheim AT, Hariz MI, Lindberg M. (1998) Assessment of ability/disability in patients treated with chronic thalamic stimulation for tremor. *Movement Disorders*, 13: 78-83.

Harwood RH, Rogers A, Dickinson E, Ebrahim S. (1994a) The London handicap scale, a new outcome measure for chronic disease. *Quality in Health Care*, 3: 11-16.

Harwood RH, Jitapunkul S, Dickinson E, Ebrahim S. (1994b) Measuring handicap: motives, methods and a model. *Quality in Health Care*, 3: 53-57.

Hasler D. (1981) The use of the gymnastic ball.*Therapy.*

Hauptvogel H, Poser S, Orthner H, Roeder F. (1975) Indikationen zur stereotaktishen Operation bei Patienten mit multipler Sklerose. *Journal of Neurology*, 210: 239-251.

Heller A, Wade D, Wood VA, Sunderland A, Langton Hewer R, Ward E. (1987) Arm function after stroke:measurement and recovery over the first 3 months. *Journal of Neurolgy, Neurosurgery and Psychiatry*, 50: 714-719.

Hewer RL, Cooper R, Morgan H. (1972) An investigation into the value of treating intention tremor by weighting the affected limb. *Brain*, 95: 579-590.

Hirai T, Miyazaki M, Nakajima H, Shibazaki T, Ohye C. (1983) The correlation between tremor characteristics and predicted volume of effective lesion in stereotaxic VIM-thalamotomy. *Brain*, 106: 1001-1018.

Hitchcock E, Flint GA, Gutowski NJ. (1987) Thalamotomy for movement disorders: a critical appraisal. *Acta Neurochir*, 61-65.

Holmes G. (1904) On certain tremors in organic cerebral lesions. *Brain*, 27: 327-375.

Holmes G. (1917) The symptoms of acute cerebellar injuries due to gunshot injuries. *Brain*, 40: 461-535.

Holmes J, Madgwick T, Bates D. (1995) The cost of multiple sclerosis. *British Journal of Medical Economics*, 8: 181-193.

Holmes J, Young C, Reti M. (1998) Quality of life in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, 64:

Hooper J, Taylor R, Pentland B, Whittle IR. (1998). Rater reliability of Fahn's tremor rating scale in patients with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation*, 79: 1076-1079.

Hooper J, Whittle IR. (1998) Long-term outcome after thalamotomy for movement disorders in multiple sclerosis. *Lancet*, 352: 1984.

Howison M, Perella J A, Gordon D. (1978) *Willard and Spackman's Occupatioanl Therapy,* Philadelphia, J.B. Lippincott.

Hubble JP, Busenbark KL, Wilkinson MD, Penn RD, Lyons K, Koller WC. (1996) Deep brain stimulation for essential tremor. *Neurology*, 46: 1150-1153.

Improvement of severe postural cerebellar tremor in multiple sclerosis by chronic thalamic stimulation. *Movement Disorders*, 11: 489-494.

Information and Statistics Division, NHS in Scotland, Trinity Park House, South Trinity Road, Edinburgh EH5 3SQ.

International Classification of Impairment, Activities and Participation-ICIDH-2. (1997) A Manual of Dimensions of Disablement and Function. *World Health Organisation*. Geneva.

International Classification of Impairments, Disabilities and Handicaps-ICIDH. (1980) *World Health Organisation*. Geneva.

Iriarte J, deCastro P. (1994) Proposal of a new scale for assessing fatigue in patients with multiple sclerosis. *Neurologia,* 11:210-215.

Iriarte J, Carreno M, deCastro P. (1996) Fatigue and functional systems involvement in multiple sclerosis. *Neurologia*, 11: 210-215.

Jacobs LD, Cookfair DL., and Rudick RA. (1994) Results of a phase III trial of intramuscular recombinant beta interferon as treatment for multiple sclerosis. *Annals of Neurology* 36, 259.

Jankovic J, Cardoso F, Grossman R, Hamilton W. (1995) Outcome after stereotactic thalamotomy for parkinsonian, essential, and other types of tremor. *Neurosurgery*, 37: 680-685.

Jeannerod M. (1984) The timing of natural prehension movements. *Journal of Natural Prehension Movements*, 16: 235-254.

Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. (1969) An objective and standardised test of hand function. *Archives of Physical Medicine and Rehabilitation*, 50: 311-319.

Jebsen RH, Griffith E, Long E, Fowler R. (1971) Function of 'normal' hand in stroke patients. *Archives of Physical Medicine and Rehabilitation*, April: 170-174.

Johnson KP, Brooks BR, Cohen JA. (1995) Copolymer I reduces the relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multi-center, double-blind, placebo-controlled trial. *Neurology*, 45: 1268-1276.

Johnston M. (1992) Measurement standards for interdisciplinary medical rehabilitation. *Archives of Physical Medicine and Rehabilitation*, 73: 3-15.

Jones L. (1986) The evaluation of the Jebsen test: reliability, validity and usefulness as a measure in neurological patients. *British College of Occupational Therapists*-fellowship thesis.

Jones L, Lewis Y, Harrison J, Wiles CM. (1996) The effectiveness of occupational therapy and physiotherapy in patients with multiple sclerosis with ataxia of the upper limb and trunk. *Clinical Rehabilitation*, 10: 277-282.

Jonsson A, Dock J, Ravnborg MH. (1996) Quality of life as a measure of rehabilitation outcome in patients with multiple sclerosis. *Acta Neurologica Scandinavia*, 93: 229-235.

Kerlinger FN. (1986) *Foundations of Behavioural Research,* 3rd edn. New York, Holt, Rinehart and Winston.

Koller WC. (1984) Pharmacological trials in the treatment of cerebellar tremor. *Archives of Neurology*, 41:280-281.

Kraft GH, Freal JE, Coryell JK. (1986) Disability, disease duration and rehabilitation needs in multiple sclerosis; patient perspectives. *Archives of Physical Medicine and Rehabilitation*, 67: 164-168.

Krauss JK, Mohadjer M, Nobbe F, Mundinger F. (1994) The treatment of post-traumatic tremor by stereotactic surgery. *Journal of Neurosurgery*, 80: 810-819.

Krauss JK, Mundinger F. (1996) Thalamic stimulation for severe action tremor after lesion of the superior cerebellar peduncle. *Journal of Neurology, Neurosurgery and Psychiatry*, 2: 234.

Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. (1988) Fatigue in multiple sclerosis. *Archives of Neurology*, 45: 435-437.

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. (1989) The Fatigue Severity Scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, 46: 1121-1123.

Kurtzke J. (1981) A proposal for a uniform minimal record of disability in multiple sclerosis. *Acta Neurologica Scandinavia*, 64: 110-129.

Kurtzke JF. (1983) Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, 33: 1444-1452.

Kurtzke J. (1991) Multiple sclerosis: changing times. *Neuroepidemiology*, 10: 1-8.

Labi M, Gresham G, Rathey U. (1982) Hand function in osteoarthritis. *Archives of Physical Medicine and Rehabilitation*, 63: 438-440.

Lang AET, Fahn S. (1989) Assessment of Parkinson's Disease. In: Munsat TL (Eds). *Quantification of neurologic deficit.* Stoneham, MA 02180, Butterworths, 285-309.

Lankhorst GJ, Jelles F, Smits RCF, Polman CH, Kuik DJ, Pfennings LEM, Cohen L, van der Ploeg HM, Vleugels L. (1996) Quality of life in multiple sclerosis: the disability and impact profile. *Journal of Neurology*, 243: 469-474.

Layward L, Dytrych L, Beresford A. (1989) Symptoms in MS: patient perspective. Multiple Sclerosis, 4 (1): 8.

Lenz FA, Kwan HC, Martin RL, Tasker RR, DostrovskyJ.O., Lenz YE. (1994) Single unit analysis of the human ventral thalamic nuclear group: tremor-related activity in functionally identified cells. *Brain*, 117: 531-543.

Liang MH, Jette AM. (1981) Measuring functional ability in chronic arthritis; a critical review. *Arthritis and Rheumatology*, 24: 80-86.

Liu X, Miall C, Aziz TZ. (1997) Analysis of action tremor and impaired control of movement velocity in multiple sclerosis during visually guided wrist tracking tasks. *Movement Disorders*, 12: 992-999.

Lublin FD, Reingold SC. (1996) Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology*, 46: 907-911.

Mahoney FI, Barthel DW. (1965) Functional evaluation; the Barthel Index. *Maryland State Medical Journal*, 14: 61-65.

Mathiowetz V, Weber K, Kashman N, Volland G. (1985) Adult norms for the nine hole peg test of finger dexterity. *Occupational Therapy Journal of Research*, 5: 24-38.

Matson RR, Brooks NA (1977) Adjusting to multiple sclerosis; an exploratory study.

Matthews B. (1988) Symptoms and Signs of Multiple Sclerosis. In:Compston, A, Ebers, G, Lassman, H et al (Eds). *MaAlpine's Multiple Sclerosis.* Third edn. Edinburgh, Churchill Livingstone.

McAlpine D, Compston ND, Lumsden CE. (1955) *Multiple Sclerosis,* Edinburgh, Churchill Livingston.

McDonald WI, Thompson AJ. (1997) How many kinds of multiple sclerosis are there? *Multiple Sclerosis-Clinical Challenges and Controversies.* London, Martin Dunitz.

McDonald WI, Halliday AM. (1977) Diagnosis and classification of MS. *British Medical Bulletin* 33:4-8.

Medical Research Council Alzheimer's Disease Workshop Steering Committee. (1989) Recommended minimum data to be collected in research studies on Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 52: 693-700.

Monks J. (1989) Experiencing symptoms in chronic illness: fatigue in multiple sclerosis. *International Disability Studies*, 11: 78-83.

Morgan MH, Hewer RL, Cooper R. (1999) Application of an objective method of assessing intention tremor: a further study on the use of weights to reduce intention tremor. *Journal of Neurology, Neurosurgery and Psychiatry*, 38: 259-264.

Murphy N, Confavreux C, Haas J, Konig N, Roullet E, Sailer M, Swash M, Young C, Merot J-L. (1998) Quality of life in multiple sclerosis in France, Germany, and the United Kingdom. *Journal of Neurology, Neurosurgery and Psychiatry*, 65: 460-466.

Murray TJ. (1995) The psychosocial aspects of multiple sclerosis. *Clinical Neurology*, 13: 197-223.

Nakamura R, Kamakura K, Tadano Y, Hosodo Y, Nagata N, Tsuchiya K, Iwata M, Shibasaki H. (1993) MR imaging findings of tremors associated with lesions in cerebellar outflow tracts: report of two cases. *Movement Disorders*, 8: 209-212.

Narabayashi H. (1986) Tremor: its generating mechanisms and treatment. In: Vinken PJ, Bruyen HL, Klawans HL (Eds). *Handbook of Clinical Neurology.* Amsterdam, Elsevier Science Publishers, Vol. 4: 597-607.

Narabayashi H. (1992) Analysis of intention tremor. *Clinical Neurology and Neurosurgery*, 94 (Suppl): 130-132.

Netten, A and Dennett, J. (1996) *Unit costs of health and social care.* University of Kent at Canterbury, Personal Social Service Research Unit.

Nguyen J-P, Degos J-D. (1993) Thalamic stimulation and proximal tremor. *Archives of Neurology*, 50: 498-500.

Nguyen J-P, Feve A, Keravel Y. (1996) Is electrostimulation preferable to surgery for upper limb ataxia? *Current Opinion in Neurology*, 9: 445-450.

Noseworthy JH, Vandervoort MK, Hopkins M, Ebers GC. (1989) A referendum on clinical trial research in multiple sclerosis: the opinion of the participants of the Jekyll Island workshop. *Neurology*, 39: 977-981.

Noseworthy JH, Vandervoort MK, Wong CJ, Ebers GC. (1990) Interrater variability with the Expanded Disability status scale (EDSS) and functional systems (FS) in a multiple sclerosis clinical trial. *Neurology*, 40: 971-974.

Notermans NC, van Dijk GW, van der Graaf Y, Wokke JHJ. (1994) Measuring ataxia: quantification based on the standard neurological examination. *Journal of Neurology, Neurosurgery and Psychiatry*, 57: 22-26.

Oyster C K, Hanten W P, Llorens L A. (1987) *Introduction to research: a guide for the health science professional,* London, J.B. Lippincott Company.

Panikoff L. (1983) Recovery trends of functional skills in head-injured adults. *American Journal of Occupational Therapy*, 37: 735-743.

Peyser JM, Rao SM, LaRocca NG, Kaplan E. (1990) Guidelines for neuropsychological research in multiple sclerosis. *Archives of Neurology*, 47: 94-97.

Polgar S, Thomas S A. (1991) *Introduction to research in the health sciences,* Second edn. London, Churchill Livingstone.

Pollack P, Benabid AL, Gervason CL. (1993) Long-term effects of chronic stimulation of the ventral intermediate thalamic nucleus in different types of tremor. In: Narabayashi, H, Nagatsu, T, Yanagiasawa, N, Mizuno, Y (Eds). *Advances in Neurology.* New York, Raven Press, Ltd., 408-413.

Poser CM, Paty DW, Schienberg L, McDonald I, Davis F, Ebers G, Johnson KP, Sibley WA, Silberberg DH, Tourellotte WW. (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology*, 13: 227-231.

Prablanc C, Echalleir JF, Komilis E, Jeannerod M. (1979) Optimal response of eye and hand motor systems in pointing at a visual target. 1.Spatio-temporal characteristics of eye and hand movements and their relationship when varying the amount of visual performance. *Biological Cybernetics*, 35: 113-124.

Radatz M, Scott R, Boulton C, Silburn P, Aziz T. (2000) Functional outcome after unilateral and bilateral pallidotomy for Parkinson's disease. *British Journal of Neurosurgery*, 14: 84.

Rao SM. (1986) Neuropsychology of multiple sclerosis: a critical review. *Journal of Clinical Experimental Neuropsychology*, 8: 503-542.

Rice GPA, Lesaux J, Vandervoort P, Macewan L, Ebers GC. (1997) Ondansetron, a 5-HT3 antagonist, improves cerebellar tremor. *Journal of Neurology, Neurosurgery and Psychiatry*, 62: 282-284.

Riise T. (1997) Is the incidence of multiple sclerosis increasing? In:Thompson AJ, Polman C, Hohlfield R (Eds). *Multiple Sclerosis-Clinical Challenges and Controversies.* London, Martin Dunitz.

Roberts MHW, Martin JP, McLellan DG. (1991) The prevalence of multiple sclerosis in Southampton and South West Hampshire Health Authority. *Journal of Neurology, Neurosurgery and Psychiatry*, 54: 55-59.

Rood M. (1962) Use of sensory receptor to activate, facilitate and inhibit motor response, automatic and somatic in developmental sequence. In: Sattley C (Eds). *Approaches to treatment in patients with neuromuscular dysfunction.* Duburque, IA, Brown Book Co.

Rothstein JR. (1993) Reliability and validity: implications for research. In: Bork CE (Eds). *Research in Physical Therapy.* Philadelphia, J.B. Lippincott Company, 18-36.

Rothwell PM. (1998) Quality of life in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, 65: 433.

Runmarker B, Andersen O. (1993) Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. *Brain*, 116: 117-134.

Sabra AF, Hallet M. (1984) Action tremor with alternating activity in antagonist muscles. *Neurology*, 34: 151-156.

Sadovnik AD, Remick RA, Allen J, Swartz E, Yee IML, Eisen K. (1996) Depression and multiple sclerosis. *Neurology*, 46: 628-632.

Sandell H. and Thompson AJ. (1999) Management of severe tremor in MS- a proposed decision pathway. *Multiple Sclerosis-Clinical and Laboratory Research*, 4 (1).

Sandell H., Porter B, Thompson AJ. (1999) Evaluation of thalamic stimulation in multiple sclerosis- a qualitative pilot study. *Multiple Sclerosis-Clinical and Laboratory Research*, 5 (1).

Schaltenbrand G, Wahren W. (1977) *Atlas for Stereotaxy of the Human Brain,* 2nd revised and enlarged edition : Stuttgart, Thieme.

Schiffer RB, Babigian HM. (1984) Behavioural disorders in multiple sclerosis, temporal lobe epilepsy and amyotrophic lateral sclerosis. an epidemiologic study. *Archives of Neurology*, 41: 1067-1069.

Schimoyama I, Ninchoji T, Uemura K. (1990) The finger-tapping test. *Archives of Neurology*, 47: 681-684.

Schuurman PR, Bosch DA, Bossuyt PM, Bonsel GJ, van Someren EJ, de Bie RM, Merkus MP, Speelman JD. (2000) A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *New England Journal of Medicine*, 342: 461-468.

Seaby L, Torrance G. (1992) Reliability of a physiotherapy functional assessment used in a rehabilitation setting. *Physiotherapy Canada*, 41: 264-271.

Sechi GP, Zuddas M, Piredda M, Agnetti V, Sau G, Piras ML, Tanca S, Rasati G. (1989) Treatment of cerebellar tremors with carbamazepine: A controlled trial with long-term follow-up. *Neurology*, 39: 1113-1115.

Shallice T and Evans ME. (1978) The involvement of the frontal lobes in cognitive estimation. *Cortex,* 14: 294-303.

Shannon, C. (1999) An introduction to MS for health and social care professionals. London, *Multiple Sclerosis Society of Great Britain and Northern Ireland.*

Shazadi S, Tasker R, Lozano A. (1996) Thalamotomy for essential and cerebellar tremor. *Stereotactic Functional Neurosurgery*, 65: 11-17.

Siegfried J. (1993) Theraputic stereotactic procedures on the thalamus for motor movement disorders. *Acta Neurochir* (Wein), 124: 14-18.

Silberberg D H. (1977) Multiple Sclerosis. In: Goldensah ES, Appell SH (Eds). *Scientific Approaches to Clinical Neurology.* Vol.1 Philadelphia, Lea and Febiger, 299-324.

Skilbeck C, Wade D, Langton Hewer R, Wood V. (1983) Recovery after stroke. *Journal of Neurology, Neurosurgery and Psychiatry* , 45:5-8.

Smith MT, Baer GD. (1999) Achievement of simple mobility milestones after stroke. *Archives of Physical Medicine and Rehabilitation,* 80:442-447.

Spaulding SJ, McPherson JJ, Strachota E, Kuphal M, Ramponi M. (1988) Jebsen hand function test: Performance of the uninvolved hand in hemiplegia and of right-handed, right and left hemiplegic persons. *Archives of Physical Medicine and Rehabilitation*, 69: 419-422.

Speelman JD, Van Manen J. (1984) Stereotactic thalamotomy for the relief of intention tremor of multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, 47: 596-599.

Speelman JD, Schuurman MD, De Bie RMA, Bosch DA. (1998) Thalamic surgery and tremor. *Movement Disorders*, 3: 103-106.

Sprangers MAG, Aaronson NK. (1992) The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. *Journal of Clinical Epidemiology*, 45: 743-760.

Sutherland J. (1982) *Progress in rehabilitation. Multiple Sclerosis,* London, Macmillan, 45-58.

Swingler RJ, Compston DAS. (1988) The prevalence of multiple sclerosis in South East Wales. *Journal of Neurology, Neurosurgery and Psychiatry*, 51: 1520-1524.

Syndulko K, Tourtellotte WW, Baumhefner RW, Ellison GW, Myers LW, Belendiuk G, Krondraske GV. (1993) Neuroperformance evaluation of multiple sclerosis disease progression in a clinical trial: implications for neurological outcomes. *Journal of Neurorehabilitation*, 7: 153-176.

Taha JM, Janszen MA, Favre J. (1999) Thalamic deep brain stimulation for the treatment of head, voice and bilateral limb tremor. *Journal of Neurosurgery*, 91: 68-71.

Taylor R. (1997) Validation of a brief neuropsychological screening test: Scottish Home and Health department Internal Research Report, unpublished.

Thompson AJ., Kermode AG., and MacManus DG. (1990) Patterns of disease activity in multiple sclerosis: clinical and magnetic resonance imaging study. British *Medical Journal* 300, 631-634

Tomlinson F, Kelly PJ, Jack CRJ. (1991) Sequential magnetic resonance imaging following stereotactic radiofrequency ventralis lateralis thalamotomy. *Journal of Neurosurgery*, 74: 579-584.

Tourtellotte WW, Syndulko K. (1989) Quantifying the neurologic examination:principle constraints and opportunities. In: Munsat TL (Ed). *Quantification of Neurologic Deficit.* Butterworth, 7-16.

Tranchant C, Bhatia KP, Marsden CD. (1995) Movement disorders in multiple sclerosis. *Movement Disorders*, 10: 418-423.

Trelles L, Trelles JO, Castro C, Altamirano J, Benaquen MN. (1984) Successful treatment of two cases of intention tremor with clonazepam. *Annals of Neurology*, 16: 621.

Van Diemen HA. (1999) The effect of 4-aminopyridine on clinical signs in multiple sclerosis: a randomised, placebo-controlled, double-blind, cross-over study. *Annals of Neurology*, 32: 123-130.

Van Manen J. (1974) Stereotactic operations in cases of hereditary and intentional tremor. *Acta Neurochir* (Wein), 21: 49-55.

Verkerk PH, Schouten JP, Oosterhuis HJGH. (1990) Measurement of hand coordination. *Clinical Neurology and Neurosurgery*, 92: 105-109.

Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. (1995) A health-related quality of life measure for multiple sclerosis. *Quality of Life Reserve*, 4: 187-206.

Vickrey BG, Hays RD, Genovese BJ, Myers LW, Ellison GW. (1997) Comparison of generic to disease-targeted health related quality of life measures for multiple sclerosis. *Journal of Clinical Epidemiology*, 50: 5457-5469.

Villagra F, Lyons K, Koller WC, Wilkinson SB, Overman J, Hubble JP, Busenbark K, Dubinsky R. (1996) Lack of rebound effect on tremor in Parkinson's disease and essential tremor patients that have undergone VIM thalamic stimulation. *Neurology* 46, 372.

Voss D E. (1972) Proprioceptive neuromuscular facilitation: the PNF method. In: Pearson, P H (Ed). *Physical Therapy Services in the Developmental Disabilities.* Springfield, Charles C. Thomas,

Wade D. (1992) In: Wade D. (Ed). *Measurement in Neurological Rehabilitation.* Oxford, Oxford University Press.

Wasielewski PG, Burns JM, Koller WC. (1998) Pharmacological treatment of tremor. *Movement Disorders*, 13: 90-99.

Wechler D. (1981) Wechler *Adult Intelligence Scale revised.* The Psychological corporation, New York.

Webster DD. (1968) Critical analysis of the disability in Parkinson's disease. *Modern Treatment*, 5: 257-282.

Weigl D. (1981) On the psycology of the so-called process of abstraction. *Journal of Abnormal movements and Social Psychology,* 36: 3-33.

Weiner W, Lang A. (1989) *Movement disorders. A comprehensive survey,* New York, Futura Publishing Company.

Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, Ebers GC. (1989) The natural history of multiple sclerosis: a geographically based study. 1. Clinical course and disability. *Brain*, 112: 133-146.

Weinshenker BG, Rice GP, Noseworthy JH. (1991) The nature of multiple sclerosis: a geographically based study. 3 multivariate analysis of predictive factors and models of outcome. *Brain*, 114: 1045-1056.

Weinshenker B G. (1997) The Natural History of MS. In: Raine CS, McFarland HF, Tourtellotte WW (Eds). *Multiple Sclerosis-Clinical and Pathogenetic Basis.* London, Chapman and Hall Medical.

Weinshenker BG. (1992) A double-blind, randomized, crossover trial of pemoline in fatigue associated with multiple sclerosis. *Neurology*, 42: 1468-1471.

Weinshenker BG, Issa M, Baskerville J. (1996) Long term and short term outcome of multiple sclerosis. A 3-year follow-up study. *Archives of Neurology*, 53: 353-358.

Whitaker JN, McFarland HF, Rudge P, Reingold SC. (1995) Outcome assessment in multiple sclerosis trials: a critical analysis. *Multiple Sclerosis*, 37-47.

Whitaker JN, Mitchell GW. (1997) Clinical Features of Multiple Sclerosis. In: Raine CS, McFarland HF, Tourtellotte WW (Eds). *Multiple Sclerosis Clinical and Pathogenetic Basis.* London, Chapman and Hall Medical.

Whittle IR, Haddow LJ. (1995) CT guided thalamotomy for movement disorders in multiple sclerosis: problems and paradoxes. *Acta Neurochirurgica* - Supplementum, 64: 13-16.

Whittle IR, Hooper J, Pentland B. (1998). Thalamic deep brain stimulation for movement disorders due to multiple sclerosis. *Lancet*, 351: 109-110.

Willoughby EW, Paty DW. (1998) Scales for rating impairment in multiple sclerosis: a critique. *Neurology*, 38: 1793-1798.

Zigmund AS, Snaith RP. (1983) The hospital anxiety and depression scale. *Acta Psychiatry Scandinavia*, 67: 361-370.

APPENDICES

APPENDIX 1

Table 1.1. Summary of thalamotomy patients'pre-operative status, MS subytpe and tremor characteristics

					TREMOR CHARACTERISTICS			
Patient	Age	MS subtype	MS (years)	Duration (months)	Severity	Type	Location	Initial result (post-op)
1	43	chron prog	7	12	severe	rubral	head,trunk,ULs	good
2	62	chron prog	13	20	severe	act/int	left UL	unchanged
3	36	chron prog	6	5	severe	rubral	head,trunk,ULs	good
4	36	chron prog	4	36	severe	rubral	head,trunk,ULs	good
5	32	chron prog	2	20	severe	rubral	head,trunk,ULs	good
6	30	chron prog	13	7	severe	rubral	head,trunk,ULs	good
7	35	relapse/remit	17	20	severe	rubral	head,trunk,ULs	good
8	34	chron prog	3	18	severe	rubral	head,trunk,ULs	good
9	32	chron prog	3	15	severe	rubral	head,trunk,ULs	good
10	52	relapse/remit	7	84	severe	act/int	rightUL	excellent

Table 1.2 Summary of thalamotomy paitents' outcome or functional result at last review, and duration of follow up

	PRE-OP STATUS	CURRENT STATUS	
Patient	Bartel Index (0-20)	Bartel Index (0-20)	Follow up/suvival time (months post-op)
1	4	dead	4
2	6	0	73
3	8	0	52
4	8	dead	9
5	9	0	62
6	8	0	56
7	9	0	56
8	6	dead	18
9	7	dead	20
10	10	15	44

APPENDIX 2

FAHN'S TREMOR RATING SCALE

Part A

NAME:_____ HOSP. #:_____

DIAGNOSIS:_____ AGE:_____ SEX:_____ R/L handed

DATE:_____

	Rest	Post.	Act./Int.	TOTAL
1. Face tremor		~~xxxxx~~	xxxxxx	
2. Tongue tremor			xxxxxx	
3. Voice tremor	xxxx	xxxxx		
4. Head tremor			xxxxxx	
5. RUE tremor				
6. LUE tremor				
7. Trunk tremor			xxxxxx	
8. RLE tremor				
9. LLE tremor				
			SUBTOTAL A:	

List of Medications

10. Handwriting (dominant only)

Comments:

	right	left	TOTAL
11. Drawing A:			
12. Drawing B:			
13. Drawing C:			
14. Pouring			
		SUBTOTAL B:	

FUNCTIONAL DISABILITIES DUE TO TREMOR

15. Speaking		
16. Eating		
17. Drinking		
18. Hygiene		
19. Dressing		
20. Writing		SUBTOTAL C:
21. Working		TOTAL SCORE: _____

Figure 17.1. Tremor rating scale.

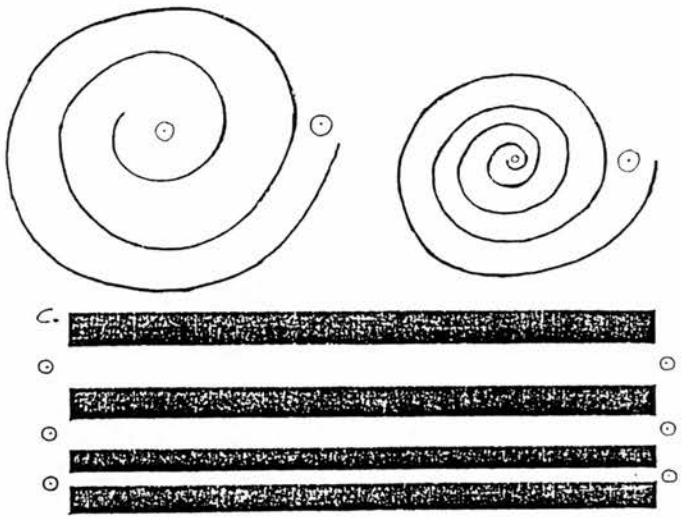
Part B

NAME: _____ DATE: _____

HANDWRITING: This is a sample of my best handwriting.
Signature Date.

DRAWINGS: with right/left hand

A. B.



C.

Figure 17.1. *Continued.*

Part C

CALCULATION

Total score/ max. possible score: / % SEVERITY
(The maximum score possible is 144)

GLOBAL ASSESSMENT BY EXAMINER: (Examiner's initials:)

0 = No functional disability.
1 = Mild disability. 1-24% impaired.
2 = Moderate disability. 25-49% impaired.
3 = Marked disability. 50-74% impaired.
4 = Severe disability. 75-100% impaired.

SCORE: _____

GLOBAL ASSESSMENT BY PATIENT:

0 = No functional disability.
1 = Mild disability. 1-24% impaired.
2 = Moderate disability. 25-49% impaired.
3 = Marked disability. 50-74% impaired.
4 = Severe disability. 75-100% impaired.

SCORE: _____

SUBJECTIVE ASSESSMENT BY PATIENT COMPARED TO LAST VISIT:

+3 = Marked improvement (50-100% improved)
+2 = Moderate improvement (25-49% improved)
+1 = Mild improvement (10-24% improved)
0 = Unchanged
-1 = Mild worsening (10-24% worse)
-2 = Moderate to marked worsening (25-49% worse)
-3 = Marked worsening (50-100% worse)

Figure 17.1. *Continued.*

et al., 1985) is not unreasonable, but it does not allow for quantitation of small changes or even qualification of different aspects of tremor. Combinations of accelerometry and clinical assessment from videotape recordings are also utilized (Hallett et al., 1985).

Sweet and his colleagues (Sweet et al., 1974) developed a clinical rating scale for tremor for their study evaluating the effects of propranolol in essential tremor. It was a weighted scale assigning different point values to different affected body areas. For example, this scale gives more points for arm tremor than for tongue tremor, which in turn scored higher than jaw tremor, which scored higher than head tremor. The points for the presence of tremor in each region was then multiplied by a factor (1 to 3) reflecting severity at each site, with 1 being mild, 2 moderate, and 3 marked. To the sum of these products was added a score for functional impairment. For this functional score, a weighted number was assigned to various activities, namely, handling a cup, handling food, use of hands, swallowing, talking, and walking. These points were multiplied by the severity factor used for severity of tremor.

The clinical rating scale developed by Sweet et al. (1974) was designed specifically for essential tremor and not for other tremors, such as resting tremor. Other disadvantages are a 4-point instead of a 5-point scale for severity; the lack of definitions for mild, moderate, and marked severity; and weighting dependent on the involved body site and the type of function that is impaired. Many important functional activities, such as writing and shaving, are not considered individually, but are lumped together as "use of hands." The impact of tremor on the patient's ability to work was not assessed. Moreover, voice tremor was not considered, except subjectively by the patient, as a symptom.

For these reasons the authors decided to develop a new clinical rating scale for tremor, one that could be used for quantitating rest, postural, and action/intention tremors (Table 17-1). This scale would also evaluate voice

Table 17-1. Definitions of Tremor Scale

1–9. **Tremor:** Rate tremor
1) at REST (in repose). For head and trunk, when lying down.
2) with posture holding (UE: arms outstretched, wrists mildly extended, fingers spread apart; LE: legs flexed at hips and knees), foot dorsiflexed; tongue: when protruded; head and trunk: when sitting or standing)
3) with ACTion and INTention (UE: finger to nose and other actions; LE: toe to finger in a flexed posture)

0 = None
1 = Slight (amplitude < 0.5 cm). May be intermittent.
2 = Moderate amplitude (0.5–1 cm). May be intermittent.
3 = Marked amplitude (1–2 cm)
4 = Severe amplitude (> 2 cm)

10. **Handwriting:** Have patient write the standard sentence: "This is a sample of my best handwriting," sign his or her name, and write the date.

0 = Normal
1 = Mildly abnormal. Slightly untidy, tremulous.
2 = Moderately abnormal. Legible, but with considerable tremor.
3 = Markedly abnormal. Illegible.
4 = Severely abnormal. Unable to keep pencil or pen on paper without holding hand down with the other hand.

11–13. **Drawings (A,B,C):** Ask the patient to join both points of the various drawings without crossing the lines. Test each hand, beginning with the lesser involved, *without leaning the hand or arm on the table*.

0 = Normal
1 = Slightly tremulous. May cross lines occasionally.
2 = Moderately tremulous or crosses lines frequently.
3 = Accomplishes the task with great difficulty. Many errors.
4 = Unable to complete drawing.

Table 17-1. *Continued.*

14. **Pouring:** Use firm plastic cups (8 cm tall), filled with water to 1 cm from top. Ask patient to pour water from one cup to another. Test each hand separately.

0 = Normal
1 = More careful than a person without tremor, but no water is spilled.
2 = Spills a small amount of water (up to 10% of total amount).
3 = Spills a considerable amount of water (>10–50%).
4 = Unable to pour without spilling most of the water.

15. **Speaking:** This includes spastic dysphonia if present.

0 = Normal
1 = Mild voice tremulousness when "nervous" only.
2 = Mild voice tremor, constant.
3 = Moderate voice tremor.
4 = Severe voice tremor. Some words difficult to understand.

16. **Feeding (other than liquids):**

0 = Normal
1 = Mildly abnormal. Can bring all solids to mouth, spilling only rarely.
2 = Moderately abnormal. Frequent spills of peas and similar foods. May bring head at least halfway to meet food.
3 = Markedly abnormal. Unable to cut or uses 2 hands to feed.
4 = Severely abnormal. Needs help to feed.

17. **Bringing Liquids to Mouth:**

0 = Normal
1 = Mildly abnormal. Can still use a spoon, but not if it is completely full.
2 = Moderately abnormal. Unable to use a spoon. Uses cup or glass.
3 = Markedly abnormal. Can drink from cup or glass, but needs 2 hands.
4 = Severely abnormal. Must use a straw.

18. **Hygiene:**

0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person.
2 = Moderately abnormal. Able to do everything, but with errors; uses electric razor because of tremor.
3 = Markedly abnormal. Unable to do most fine tasks, such as putting on lipstick or shaving (even with electric shaver), unless using two hands.
4 = Severely abnormal. Unable to do any fine-movement tasks.

19. **Dressing:**

0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person.
2 = Moderately abnormal. Able to do everything, but with errors.
3 = Markedly abnormal. Needs some assistance with buttoning or other activities, such as tying shoelaces.
4 = Severely abnormal. Requires assistance even for gross motor activities.

20. **Writing:**

0 = Normal
1 = Mildly abnormal. Legible. Continues to write letters.
2 = Moderately abnormal. Legible, but no longer writes letters.
3 = Markedly abnormal. Illegible.
4 = Severely abnormal. Unable to sign checks or other documents requiring signature.

21. **Working:**

0 = Tremor does not interfere with the job.
1 = Able to work, but needs to be more careful than the average person.
2 = Able to do everything, but with errors. Poorer than usual performance because of tremor.
3 = Unable to do regular job. May have changed to a different job because of tremor. Tremor limits housework, such as ironing.
4 = Unable to do any outside job; housework very limited.

APPENDIX 3

DEFINITIONS FOR FAHN'S TREMOR RATING SCALE

APPENDIX 4

MODIFIED FAHN'S TREMOR RATING SCALE

Please print or type

1. Patient Identifier _____ / _____ / _____

2. Date of Birth _____ / _____ / _____
   month day year

3. Date of Evaluation _____ / _____ / _____
   month day year

4. Enter time of day scored _____ AM _____ PM

5. Assessment Interval: ☐ Pre Implant ☐ 6 month ☐ Other, specify:_____
   ☐ 1 month ☐ 9 month
   ☐ 3 month ☐ 12 month

TREMOR RATING SCALE
PART A

1. Head tremor	0 = None 1 = Slight. May be intermittent 2 = Moderate amplitude. May be intermittent 3 = Marked amplitude 4 = Severe amplitude	REST POST KIN/INT GOAL RELATED	☐ ☐ ☐ ☐	
2. Trunk tremor	0 = None 1 = Slight. May be intermittent 2 = Moderate amplitude. May be intermittent 3 = Marked amplitude 4 = Severe amplitude	REST POST KIN/INT GOAL RELATED	☐ ☐ ☐ ☐	
3. Right Upper Extremity tremor	0 = None 1 = Slight. May be intermittent 2 = Moderate amplitude. May be intermittent 3 = Marked amplitude 4 = Severe amplitude	REST POST a) b) KIN/INT GOAL RELATED	☐ ☐ ☐ ☐ ☐	UL ext ULflex
4. Left Upper Extremity tremor	0 = None 1 = Slight. May be intermittent 2 = Moderate amplitude. May be intermittent 3 = Marked amplitude 4 = Severe amplitude	REST POST a) b) KIN/INT GOAL RELATED	☐ ☐ ☐ ☐ ☐	UL ext ULflex

Patient Identifier _____ _____ _____

Date of Birth _____ / _____ / _____
month day year

Date of Evaluation _____ / _____ / _____
month day year

PART B

5 -7 Ask the patient to join both points of the various drawings without crossing the lines. Test each hand, beginning with the dominant

5. **Drawing A**	0 = Normal 1 = Slightly tremulous. May cross lines occasionally 2 = Moderately tremulous or crosses lines frequently 3 = Accomplishes the task with great difficulty. Many errors 4 = Unable to complete drawing	Right Left	___ ___ ___
6 **Drawing B**	0 = Normal 1 = Slightly tremulous. May cross lines occasionally 2 = Moderately tremulous or crosses lines frequently 3 = Accomplishes the task with great difficulty. Many errors 4 = Unable to complete drawing	Right Left	___ ___ ___
7. **Pouring** (use firm plastic cups, about 8cm tall, filled with water to 1cm from top. Ask patient to pour water from one cup to another. Test each hand separately).	0 = Normal 1 = More careful than a person without tremor, but no water is spilled 2 = Spills a small amount of water (up to 10% of total amount) 3 = Spills a considerable amount of water (> 10-50%) 4 = Unable to pour water without spilling most of the water	Right Left	___ ___ ___

Patient Identifier _____ _____ _____

Date of Birth _____ / _____ / _____
MONTH DAY YEAR

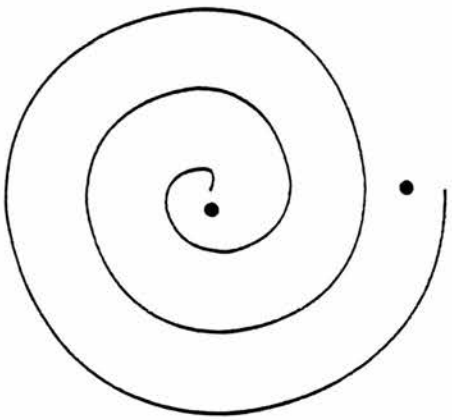
Date of Evaluation _____ / _____ / _____
MONTH DAY YEAR

DOMINANT HAND

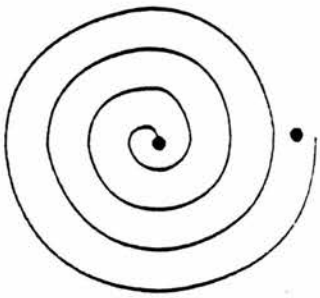
Drawings A, B and C are made with the _____ Left Hand

_____ Right Hand

DRAWING A



DRAWING B



Patient Identifier _____ _____ _____

Date of Birth _____ / _____ / _____
MONTH DAY YEAR

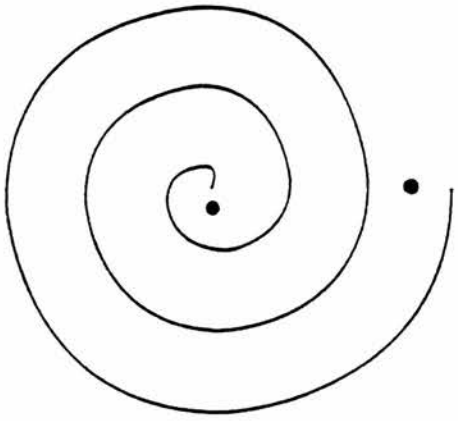
Date of Evaluation _____ / _____ / _____
MONTH DAY YEAR

NON-DOMINANT HAND

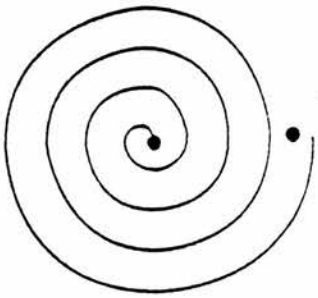
Drawings A, B and C are made with the _____ Left Hand

_____ Right Hand

DRAWING A



DRAWING B



Patient Identifier _____ _____ _____

Date of Birth _____ / _____ / _____
month day year

Date of Evaluation _____ / _____ / _____
month day year

PART C To be completed ONLY after referring to the guidelines.Scores are provided by patients (with the exception of speaking). Patients are asks to evaluate their ability to carry out these tasks using the **target arm** or both arms (if a bilateral activity) using the definitions provided.

8. Speaking
0 = Normal
1 = Mild dysarthria when "nervous" only
2 = Mild dysarthria, constant
3 = Moderate dysarthria
4 = Severe dysarthria. Some words difficult to understand.

9. Feeding other than liquids
0 = Normal
1 = Mildly abnormal. Can bring all solids to mouth, spilling only rarely
2 = Moderately abnormal. Frequent spills of peas and similar foods. May bring head at least halfway to meet food.
3 = Markedly abnormal. Unable to cut or uses two hands to feed.
4 = Severely abnormal. Needs help to feed.

10. Bringing liquids to mouth
0 = Normal
1 = Mildly abnormal. Can still use a spoon, but not if it is completely full.
2 = Markedly abnormal. Unable to use spoon; uses cup or glass
3 = Markedly abnormal. Can drink from cup or glass, but needs two hands.
4 = Severely abnormal. Must use a straw.

11. Hygiene
0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person.
2 = Moderately abnormal. Able to do everything, but with errors; uses electric razor because of tremor.
3 = Markedly abnormal. Unable to do most fine tasks, such as putting on lipstick or shaving (even with electric shaver), unless using two hands.
4 = Severely abnormal. Unable to do any fine-movement tasks.

12. Dressing
0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person.
2 = Moderately abnormal. Able to do everything, but with errors.
3 = Markedly abnormal. Needs some assistance with buttoning or other activities, such as tying shoelaces.
4 = Severely abnormal. Requires assistance even for gross motor activities.

13. Writing
0 = Normal
1 = Mildly abnormal. Legible. Continues to write letters.
2 = Moderately abnormal. Legible, but no longer writes letters.
3 = Markedly abnormal. Illegible.
4 = Severely abnormal. Unable to sign checks or other documents requiring a signature.

14. Working
0 = Tremor does not interfere with job
1 = Able to work, but needs to be more careful than the average person.
2 = Able to do everything, but with errors. Poorer than usual performance because of tremor.
3 = Unable to do regular job. May have changed to a different job because of tremor. Tremor limits housework, such as ironing.
4 = Unable to do any outside job; housework very limited.

GLOBAL ASSESSMENT

Patient Identifier _____ _____ _____

Date of Birth _____ / _____ / _____
month day year

Date of Evaluation _____ / _____ / _____
month day year

Based on assessment of tremor related disability which is calculated according to the percent of impairment in carrying out all activities of daily living and the cosmetic effect of the tremor.

GLOBAL ASSESSMENT BY EXAMINER (Circle one of the 5 levels)

0	=	No functional disability	
1	=	Mild disability	1-24% impaired
2	=	Moderate disability	25-49% impaired
3	=	Marked disability	50-74% impaired
4	=	Severe disability	75-100%impaired

GLOBAL ASSESSMENT BY PATIENT (Circle one of the 5 levels)

0	=	No functional disability	
1	=	Mild disability	1-24% impaired
2	=	Moderate disability	25-49% impaired
3	=	Marked disability	50-74% impaired
4	=	Severe disability	75-100% impaired

SUBJECTIVE ASSESSMENT BY PATIENT COMPARED TO LAST VISIT (Circle one of the 7 levels)

+3	=	Marked improvement	(50-100% improved)
+2	=	Moderate improvement	(25-49% improved)
+1	=	Mild improvement	(10-24% improved)
0	=	Unchanged	
-1	=	Mild worsening	(10-24% worse)
-2	=	Moderate to marked worsening	(25-49% worse)
-3	=	Marked worsening	(50-100% worse)

APPENDIX 5

MODIFIED FAHN'S TREMOR RATING SCALE

GUIDELINES FOR COMPLETING THE FORM

The rating scale is divided into 3 parts (A, B & C).

PART A

Part A (Scores 1-4) quantifies the tremor at test, with posture holding, and with action and intention manoeuvres, for 4 parts of the body.
Severity of tremor in each of the four body parts is rated by amplitude. Whether the tremor is intermittent or always present is not a factor in the severity score.
The definitions for tremor severity are:-

0 = None
1 = Slight, barely perceivable, maximal amplitude < 1cm, may be intermittent
2 = Moderate, amplitude 1 – 5cm, may be intermittent
3 = Marked, amplitude 5 – 10cm
4 = Severe, amplitude> 10 cm

The definitions indicate that tremors rated 1 and 2 could be either intermittent or continuous. Since larger amplitude tremors are less likely to be intermittent, the definitions for 3 and 4 severities do not list the choice for intermittence.

Tremor severity in Part A is rated for four situations: rest, maintaining a posture, performing a movement and performing a motor goal. Definitions for these 3 situations are provided for the head, trunk and limbs as follows.

Tremor:

1. **at REST (in repose)**

   Observe the head and trunk, when the patient is lying supine or with the head and trunk fully supported by head rests and back rests in the wheelchair. Observe the upper limbs, with the forearms resting on the thighs.

   NB some individuals may not be able to relax their muscles when they are positioned up against gravity even though they are supported in a wheelchair. Consequently even though they are at rest their tremor may still be evident. In this instance, one might have to assess for rest tremor with the patient supine. It is also important to allow some time to elapse for relaxation to occur (approximately 10 seconds).

2. **<u>with posture holding</u>**

Observe the head - patient sitting in chair/wheelchair with back supported but no head support.

Observe the trunk patient attempting to sit unsupported (i.e. sitting balance test). If the patient does not have static sitting balance ie. cannot hold a posture, write unable to score next to this.

Observe the UE - a) arms outstretched, wrists mildly extended, fingers spread apart.

- b) arms held with elbows flexed, shoulders abducted and fingers spread apart. Winged posture to look for "wing beating" tremor.

3. **<u>with ACTION & INTENTION</u>**

Observe the head - Whilst the patient moves their head from side to side and looks up.

Observe the trunk - Whilst the patient attempt standing and walking. If patient is unable due to lower limb involvement then observe the trunk whilst patient attempts sitting.

Observe the UE - Whilst the patient performs the finger to nose test 3x.

<u>NB</u> **Action and intention tremor are given a single score.**

4. **<u>with GOAL - related</u>**

Observe the head - Whilst the patient performs the tasks in Sec B, handwriting and card turning. Also observe them attempting to drink from a straw in a cup held by the examiner.

Observe the trunk - Whilst the patient moves from sitting to standing or if unable due to lower limb weakness observe the trunk whilst they perform the upper limb function tasks in Sec B and the subtests of the JTHF.

Observe the UL's - Whilst the patient performs the upper limb function tasks in Sec B and the subtests of the JTHF.

<u>N.B</u>. Since action/intention and goal related tremor may be superimposed on top of postural tremor it is important to determine if the activity results in a greater tremor amplitude than that seen with posture holding alone.

PART B

Part B (Scores 5 to 7) relates to action/intention and goal-related tremors of the upper limbs. Severity is determined by watching the patient draw spirals and pour water. The patient is allowed to rest their target arm on the table while they perform the tests.

Spirometry is evaluated by having the patient carry out the activities on the scoring form. Space is available for assessing each hand.

Task A }
} are the drawing of an Archimede's spiral.
Task B }

The quantification of these tasks is based on the crossing of the lines in the figure. There is less space available between the lines in task B, making the task more difficult.

Pouring water from one cup to another is also quantified. Cup size and the amount of water used in the test are specified to ensure consistency between examination events and among clinicians. The amount of water spilled is the basis for the severity grading.

PART C

Part C assesses functional ability. Its items evaluate the severity of tremor with:

- speaking
- eating (feeding)
- bringing liquids to the mouth
- hygienic care
- dressing
- working (this classification includes homemaking, as well as other jobs)

These scores with the exception of speaking, are provided by patients, who are asked to evaluate their ability to carry out these tasks by using the definitions provided. Speaking can also be evaluated by the examiner and is a global evaluation of whether the patient appears to have any difficulties with speech eg. obvious dysarthria. This is purely an observation made by the researcher and not an attempt to diagnose the cause of the speech impairement.

Unilateral upper limb activities in Part C are assessing the ***target extremity*** except for writing which evaluates the dominant hand. The bilateral activities are a global assessment of the ability to perform the task with both arms taking into consideration the functioning of the unaffected or less affected arm.

The definitions for evaluating and scoring tremor, drawing, pouring and functional ability (Parts A, B and C) are provided in Appendix 6 (Definitions for scoring the MFTRS).

Global Assessment

In addition to the quantitation of tremor through Parts A, B & C, the scoring form allows assessment of overall severity by both the patient and the examiner. This subjective global severity is based on the assessment of tremor-related disability, which is calculated according to the percent of impairment in carrying out all activities of daily living and the cosmetic effect of the tremor, which can be psychologically damaging.

Comparison Assessment

The scores obtained in Parts A, B & C and the global assessments will provide the major input of a comparison before and after implantation of DBS. However, it is also useful to obtain subjective evaluations by the patient as to the effectiveness of the stimulator. The scoring form provides definitions for the patient to carry out such a self-evaluation (see Definitions for Fahn's TRS,p- of Appendix). Patients are not permitted to refer to old scores when making a new judgement at a later assessment.

Scoring System

1. ***To obtain information relating to tremor in different areas of the body :*** the total score for each of the body areas in Part A is calculated by amalgamating the scores for the different components of tremor in each body area.

2. ***To obtain a specific evaluation of the target upper limb:*** the subtotal score for the target upper limb in Part A (out of a possible 20) plus a subtotal score for the target upper limb's performance of the tasks in Part B (out of a possible 12) plus the total score for Part C (out of a possible 28) are amalgamated giving a total possible score out of 60 for a very severely tremorous patient with no functional use of the target upper limb.

3. ***The % severity of disability can then be calculated for the target upper limb:*** the total score is expressed as a percentage

ie. $\% \text{ severity} = \frac{\text{total score}}{60} \times \frac{100}{1}$

APPENDIX 6

DEFINITIONS FOR THE CLINICAL GRADING OF THE VARIOUS COMPONENTS OF TREMOR USING THE MODIFIED FAHN'S TRS

PART A (scores 1-4)
Rating Tremor = Rate tremor amplitude

1) at REST (in repose)
For head and trunk: when fully supported in wheelchair or lying down
For UE: with forearms resting on thighs
For LE: sitting in chair

2) with POSTure holding
For head: with patient sitting with no head support.
For trunk: with patient sitting trying to achieve sitting balance with no trunk support
For UE:a) arms outstretched, wrists mildly extended, fingers spread apart
b) arms held with elbows flexed, shoulders abducted and fingers spread apart

3) with ACTion and INTention
For head Observe the head whilst the patient moves their head from side to side and looks up.
For trunk Observe the trunk whilst the patient attempt standing and walking. If patient is unable due to lower limb involvement then observe the trunk whilst patient attempts sitting.
For UE: Finger to nose test 3x and other actions, ie pouring water, drinking from a cup, the Jebsen.

4) with GOAL related
For head: observe the head whilst the patient drinks water using a straw from a beaker held in front of the patient by the examiner and also while the patient performs the upper limb functional tasks in Sec B and the subtests of the JTHF.
For trunk: observe the trunk whilst the patient moves from sitting to standing or if unable due to lower limb weakness observe the trunk whilst they perform the upper limb function tasks in Sec B and the subtests of the JTHF.

For UE: observe the head whilst the patient performs the upper limb functional tasks in Sec B and the subtests of the JTHF.

0 = None 1 = Slight, barely perceivable, maximal amplitude<1 cm, may be intermittent. 2 = Moderate, amplitude 1 – 5cm, may be intermittent. 3 = Marked, amplitude 5 – 10cm. 4 = Severe, amplitude >10cm.

PART B (scores 5-7)

5-6 **Drawings (A, B):** Ask the patient to join both points of the spirals without crossing the lines. Test each hand, beginning with the lesser involved hand

0 = Normal 1 = Slightly tremulous. May cross lines occasionally. 2 = Moderately tremulous or crosses lines frequently. 3 = Accomplishes the task with great difficulty. Many errors. 4 = Unable to complete drawing.

7. **Pouring:** Use firm plastic cups (8cm tall), filled with water to 1cm from top. Ask patient to pour water from one cup to another. Test each hand separately.

0 = Normal 1 = More careful than a person without tremor, but no water spilled. 2 = Spills a small amount of water (up to 10% of total amount). 3 = Spills a considerable amount of water (> 10 - 50%). 4 = Unable to pour water without spilling most of the water.

PART C (scores 8-14) Scores are provided by patients with the exception of speaking.

8. Speaking	0 = Normal 1 = Mild dysarthria when "nervous" only 2 = Mild dysarthria 3 = Moderate dysarthria 4 = Severe dysarthria. Some words difficult to understand.	☐
9. Feeding other than liquids	0 = Normal 1 = Mildly abnormal. Can bring all solids to mouth, spilling only rarely 2 = Moderately abnormal. Frequent spills of peas and similar foods. May bring head at least halfway to meet food. 3 = Markedly abnormal. Unable to cut or uses two hands to feed. 4 = Severely abnormal. Needs help to feed.	☐
10. Bringing liquids to mouth	0 = Normal 1 = Mildly abnormal. Can still use a spoon, but not if it is completely full. 2 = Markedly abnormal. Unable to use spoon; uses cup or glass 3 = Markedly abnormal. Can drink from cup or glass, but needs two hands. 4 = Severely abnormal. Must use a straw.	☐
11. Hygiene	0 = Normal 1 = Mildly abnormal. Able to do everything, but is more careful than the average person. 2 = Moderately abnormal. Able to do everything, but with errors; uses electric razor because of tremor. 3 = Markedly abnormal. Unable to do most fine tasks, such as putting on lipstick or shaving (even with electric shaver), unless using two hands. 4 = Severely abnormal. Unable to do any fine-movement tasks.	☐
12. Dressing	0 = Normal 1 = Mildly abnormal. Able to do everything, but is more careful than the average person. 2 = Moderately abnormal. Able to do everything, but with errors. 3 = Markedly abnormal. Needs some assistance with buttoning or other activities, such as tying shoelaces. 4 = Severely abnormal. Requires assistance even for gross motor activities.	☐
3. Writing	0 = Normal 1 = Mildly abnormal. Legible. Continues to write letters. 2 = Moderately abnormal. Legible, but no longer writes letters. 3 = Markedly abnormal. Illegible.	☐

	4 = Severely abnormal. Unable to sign checks or other documents requiring a signature.
14. Working	0 = Tremor does not interfere with job
average person.	1 = Able to work, but needs to be more careful than the
	2 = Able to do everything, but with errors. Poorer than usual performance because of tremor.
	3 = Unable to do regular job. May have changed to a different job because of tremor. Tremor limits housework, such as
ironing.	
	4 = Unable to do any outside job; housework very limited.

Based on assessment of tremor related disability which is calculated according to the percent of impairment in carrying out all activities of daily living and the cosmetic effect of the tremor.

GLOBAL ASSESSMENT BY EXAMINER (Circle one of the 5 levels)

0	=	No functional disability	
1	=	Mild disability	1-24% impaired
2	=	Moderate disability	25-49% impaired
3	=	Marked disability	50-74% impaired
4	=	Severe disability	75-100%impaired

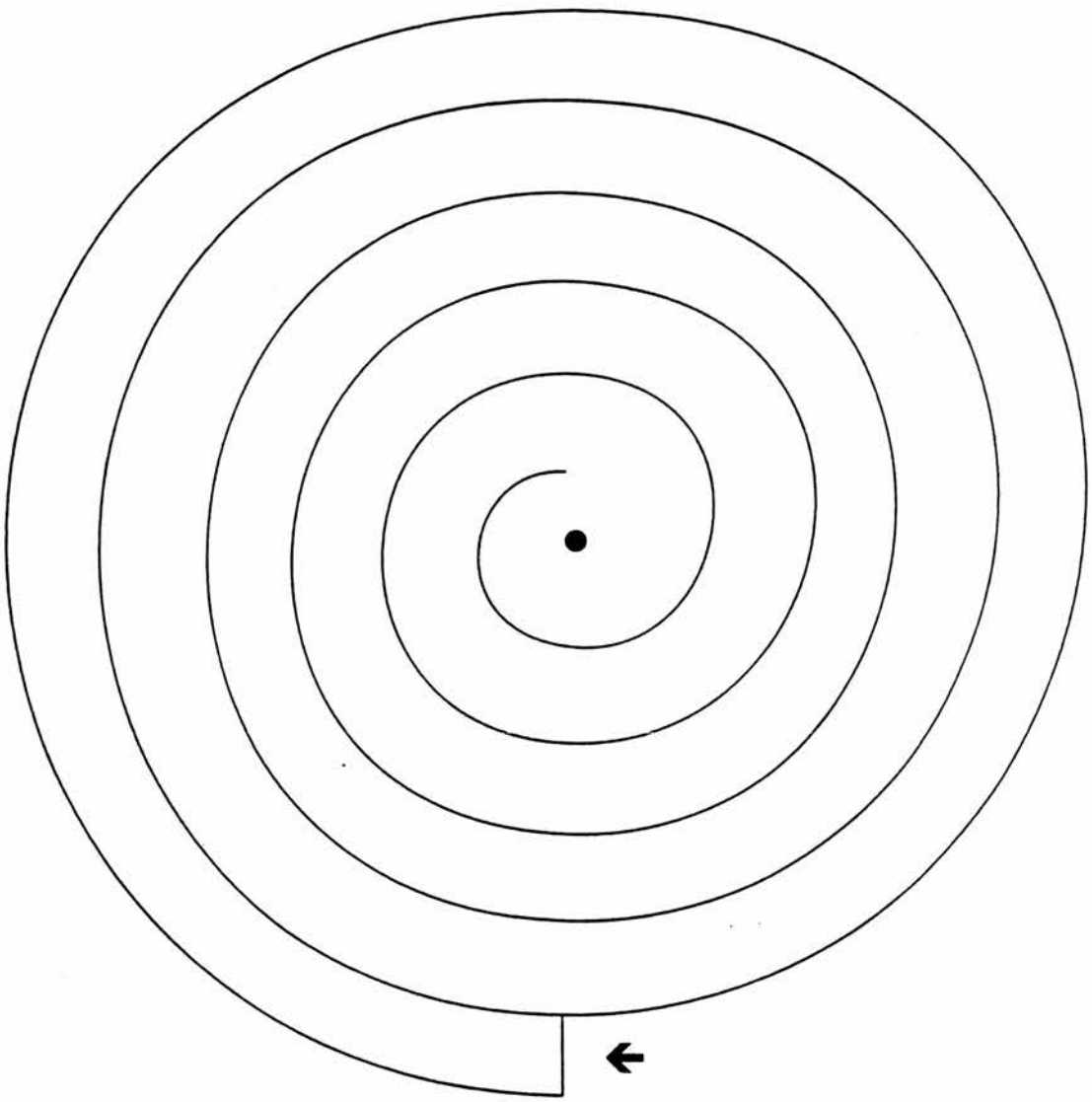
GLOBAL ASSESSMENT BY PATIENT (Circle one of the 5 levels)

0	=	No functional disability	
1	=	Mild disability	1-24% impaired
2	=	Moderate disability	25-49% impaired
3	=	Marked disability	50-74% impaired
4	=	Severe disability	75-100% impaired

SUBJECTIVE ASSESSMENT BY PATIENT COMPARED TO LAST VISIT (Circle one of the 7 levels)

+3	=	Marked improvement	(50-100% improved)
+2	=	Moderate improvement	(25-49% improved)
+1	=	Mild improvement	(10-24% improved)
0	=	Unchanged	
-1	=	Mild worsening	(10-24% worse)
-2	=	Moderate to marked worsening	(25-49% worse)
-3	=	Marked worsening	(50-100% worse)

APPENDIX 7



APPENDIX 8

JEBSEN TEST OF HAND FUNCTION

GUIDELINES FOR PERFORMING THE TEST BATTERY

Specifications for placement of test equipment and subject:

If the right hand is being assessed the perspex board (See Appendix 9 for description) should be positioned on the right hand side of the table before commencing the subtests to establish the position of the central reference point. To do this the right hand edge of the perspex board should be placed in line with the right hand edge of the table and a marker should be placed on the front edge of the table, in line with the central marker on the front edge of the board. This is the *central reference point* from which the distance to all markers placed on the table should be measured ie. markers for cards, small objects coffee jar and the perspex board.

The subject should be seated as close to the table as possible with their midline positioned inline with the central reference point on the table. Ideally the patient should be sitting on a dining chair with no arms so that they are close to the table. If they are wheelchair bound where possible the arms of the wheelchair should be removed but this will only be possible in those patients who have adequate trunk control to sit without lateral support.

Equipment required:

Clip-board, plain A4 paper, black rollerball pen, nine 5 inch by 3 inch cards, 1 pound coffee jar, 2 X 1 inch paper clips, 2 regular sized bottle tops(about 1 inch in diameter), 2 one pence pennies, 5 kidney beans, a teaspoon, 4 checkers, 5 empty baked bean cans, 5 full baked bean cans, 2 crocodile clips, a packet of self adhesive markers, a ruler and the perspex board.

Standardised procedures and instructions:

The subtest descriptions below have been written for a right-handed subject. The subtests were always presented in the same sequence and were always performed with the dominant hand first.

SUBTEST 1: WRITING

Procedure:- The subject is given a black rollerball pen and a sheet of A4 blank, unruled white paper fastened to a clip board. The sentence to be copied has 24 letters and is of third-grade reading difficulty.* The sentence is typed in capital letters and centred on a 3 by 5 inch index card. The card is presented with the typed side faced down on the table. After the articles have been arranged to the comfort of the subject (See Instructions), the card is turned over by the researcher with an immediate command to begin. The item is timed from the word "go" until the pen is lifted from the page at the end of the sentence. The item is repeated with the non dominant hand using a new sentence.

Instructions:- "Do you require glasses for reading? If so, put them on. Take this pen in your right hand and arrange everything so that it is comfortable for you to write with your right hand. On the other side of this card(indicate) is a sentence . When I

turn the card over and say 'Go' write or print the sentence as quickly and as clearly as you can using your right hand. Do you understand? Ready? Go."

- Different sentences were used when subsequent sub tests were given to an individual. Available sentences were: (1) The old man seemed to be tired. (2) John saw the red truck coming. (3) Whales live in the blue ocean. (4) Fish take air out of the water.

SUBTEST 2: CARD TURNING (simulated page turning)

Procedure:- Five 3 by 5 inch index cards, with a cross on one side only were placed in a horizontal row 2 inches apart on the table in front of the patient. Each card is oriented vertically, 5 inches from the front edge of the table. This distance is indicated on the table with a small marker stuck to the table (Fig 1A). Timing was from the word "Go" until the last card is turned over. No accuracy of placement after turning is necessary. The item was repeated with the non-dominant hand.

Instructions:- " Place your right hand on the table please. When I say 'Go' use your right hand to turn these cards over one at a time as quickly as you can beginning with this one (indicate card to extreme left). You may turn them over in any way that you wish and they need not be in a neat pattern when you finish. Do you understand? Ready? Go"

Non Dominant hand:- "Now the same thing with the left hand beginning with this one(indicate extreme right card). Ready? Go."

SUBTEST 3: SMALL COMMON OBJECTS

Procedure:- An empty 1-pound coffee can is placed directly in front of the subject, 5 inches from the front edge of the desk. Two 1-inch paper clips (oriented vertically),

two regular sized bottle tops(each one inch in diameter, placed with the inside of the cap facing up) and two one pence pennies are placed in a horizontal row to the right of the can. The paper clips are to the extreme right and the pennies nearest the can. The objects are 2 inches apart and there placement is indicated by markers stuck to the table (See Fig 1B). Timing is from the word "Go" until the sound of the last object striking the inside of the can is heard. The item is repeated with the non-dominant hand. The layout for the non dominant hand is a mirror image of the one described, with the objects to the left of the can.

Instructions:- " Place your left hand on the table please. When I say 'Go' use you right hand to pick up these objects one at a time and place them in the can as fast as you can beginning with this one (indicate paper clip on the extreme right) Do you understand? Ready? Go"

SUBTEST 4: SIMULATED FEEDING

Procedure:- Five kidney beans of approximately 5/8-inch are placed on the perspex board clamped to the table in front of the subject, 5 inches from the front edge of the table. The beans are orientated to the right of centre, parallel to and touching the upright of the board 2 inches apart. An empty one pound coffee can is placed centrally in front of the board. A regular teaspoon is provided (Fig 1C). Timing is from the word "Go" until the last bean is heard hitting the bottom of the can. The item is repeated with the non-dominant hand, the beans being placed to the left of centre.

Instructions:-" take the teaspoon in your right hand please. When I say 'Go' use your right hand to pick up the beans one at a time with the teaspoon and place them

in the can as fast as you can beginning with this one (indicate bean on the extreme right). Do you understand? Ready? Go"

Non Dominant hand:- "Now the same thing with the left hand(indicate bean on the extreme left). Ready? Go."

SUBTEST 5: CHECKERS

Procedue:- Four standard sized (one and a 1/4 inch diameter) checkers are placed in front of and touching the perspex board clamped to the table in front of the subject, 5 inches from the front edge of the table. The checkers are orientated two on either side of the centre in a 0000 configuration (Fig 1D). Timing is from the word "Go" until the fourth checker makes contact with the third checker. The fourth checker has to stay in place stacked on top of the other checkers. The item is repeated with the non-dominant hand.

Instructions:- Place your left hand on the table please. When I say "Go" use your right hand to stack your checkers on the board in front of you as fast as you can like this, one on top of the other (demonstrate). You may begin with any checker. Do you understand? Ready? Go"

SUBTEST 6: LARGE LIGHT OBJECTS

Procedure:-Five empty food cans (baked beans) are placed in front of the perspex board clamped to the table in front of the subject 5 inches from the front edge of the table. The cans are spaced 2 inches apart with the open end of the can facing down (fig1E). Timing is from the word "Go" until the fifth can has been released. The item is repeated with the non-dominant hand.

Instructions:- "Place your right hand on the table please. When I say "Go" use your right hand to stand these cans on the board in front of you, like this (demonstrate). Begin with this one (indicate the can on the extreme left). Do you understand? Ready? Go."

SUBTEST 7: LARGE HEAVY CANS

Procedure:- Five full(1 pound) cans are placed in front of the perspex board clamped to table in front of the subject, 5 inches from the front edge of the desk. The cans are spaced 2 inches apart (Fig 1E). Timing is from the word "Go" until the fifth can has been released. The item is repeated with the non-dominant hand.

Instructions:- "Now do the same thing with these heavier cans. Place your right hand on the table. When I say "Go" use your right hand to stand these cans on the board as fast as you can. Begin here (indicate can on extreme right). Do you understand? Ready? Go."

Non Dominant Hand:- " Now the same thing with your left hand beginning here (indicate can on far left). Ready? Go."

Figure 1A: placement of equipment for subtest 2 - card turning

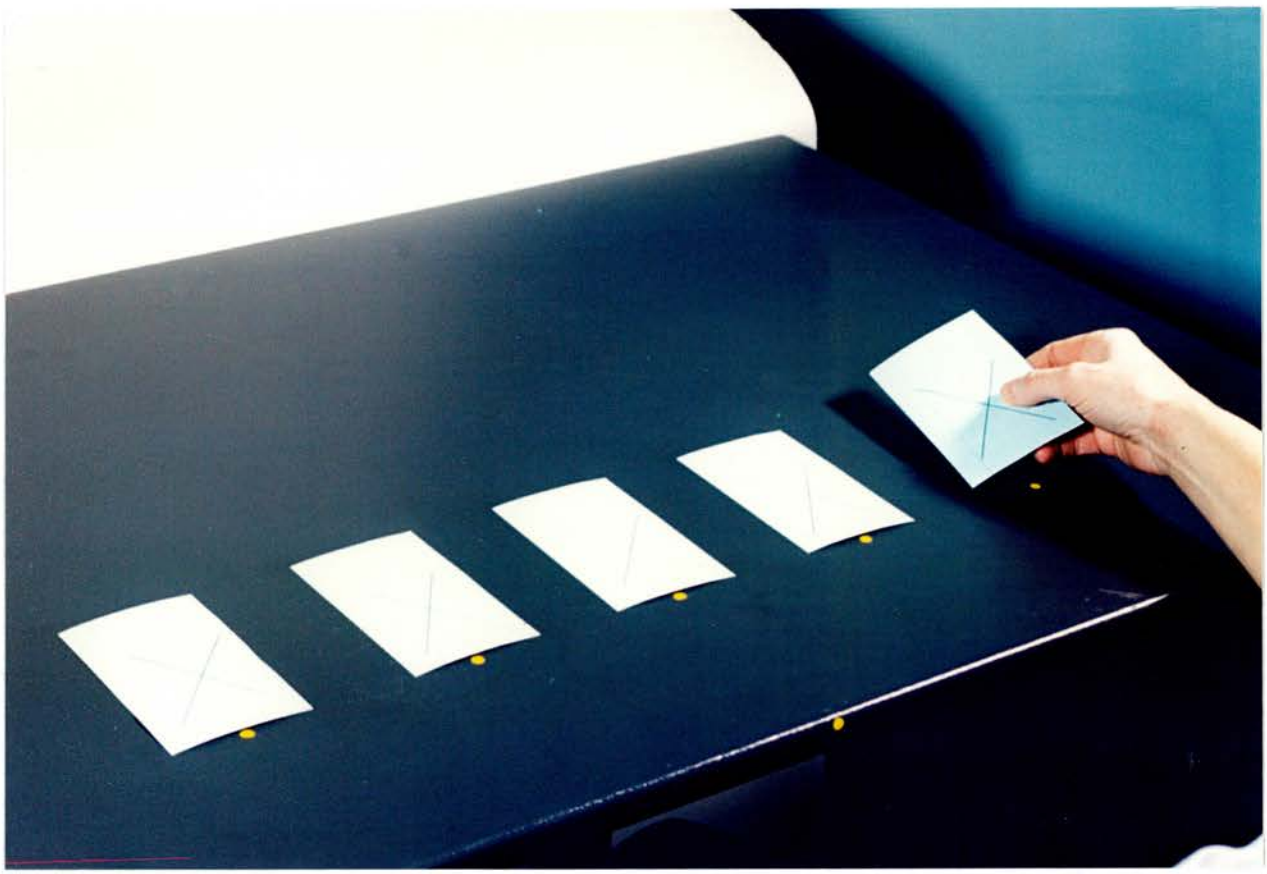


Figure 1B: placement of equipment for subtest 3 - picking up small common objects

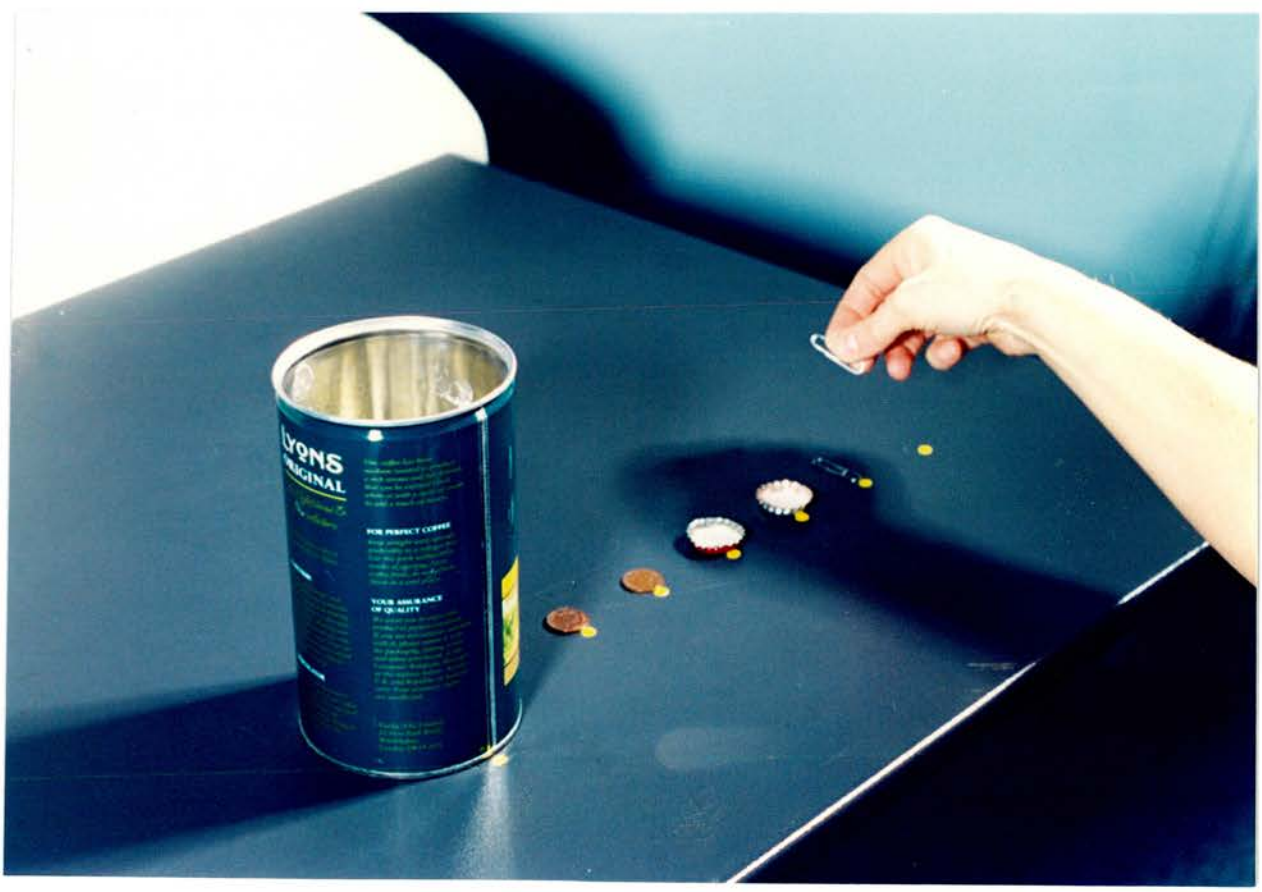


Figure 1C: placement of equipment for subtest 4 - simulated feeding

Figure 1D: placement of equipment for subtest 5 - stacking checkers

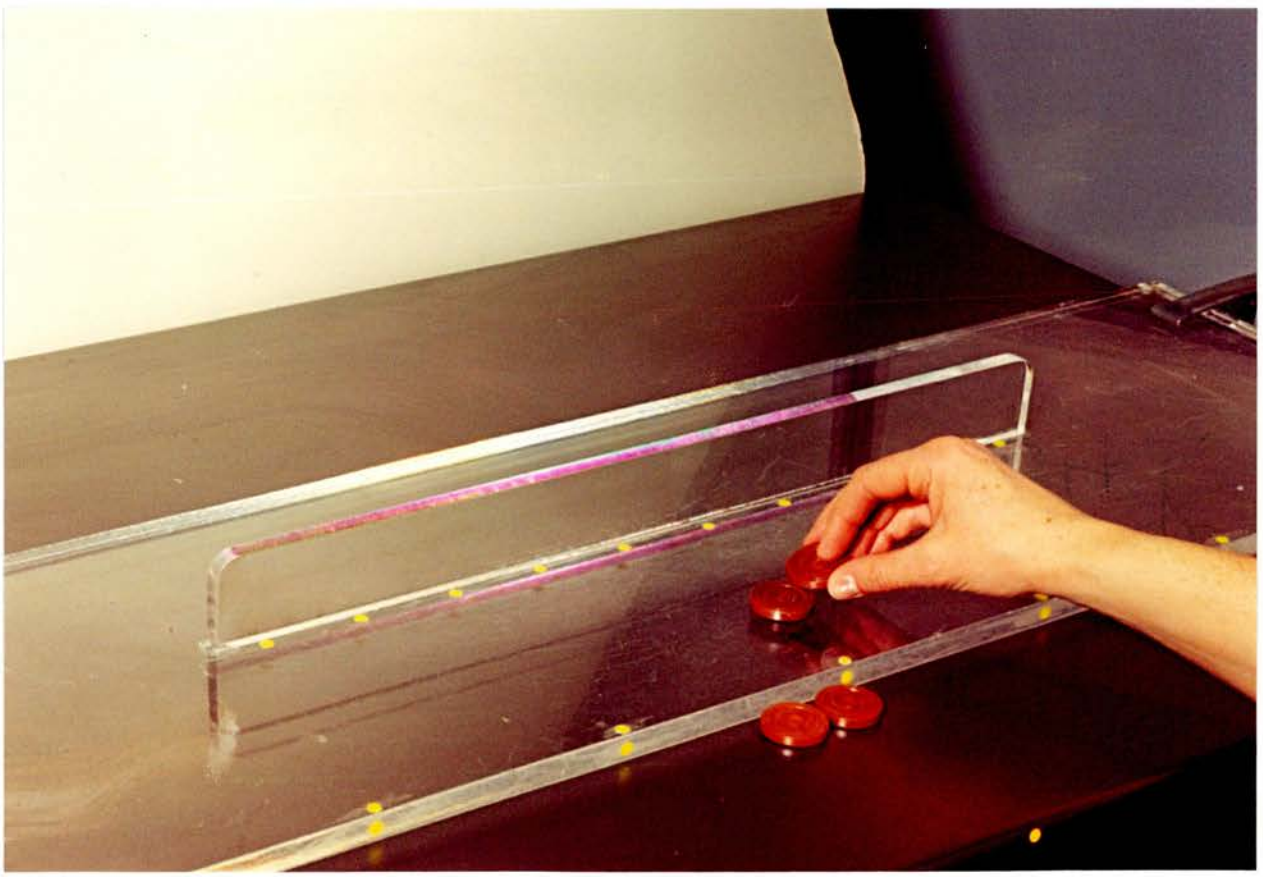
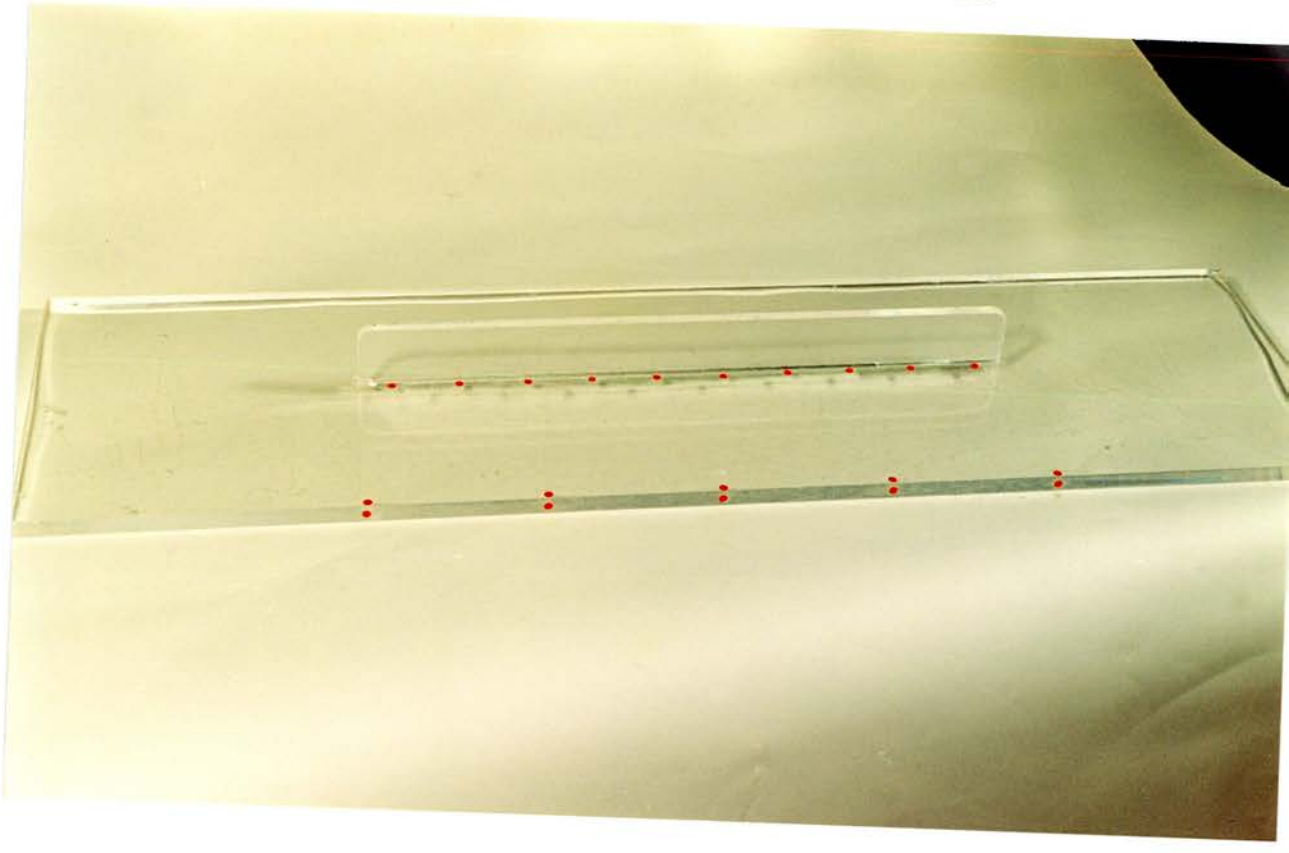


Figure 1E: placement of equipment for subtests 6 and 7- moving large objects (empty or full cans)

APPENDIX 9

DIMENSIONS OF THE JEBSEN BOARD



Dimensions of the Jebsen board:

A perspex board 100cm long, 30cm wide and 14mm thick was secured to the table with 2 crocodile clips. The front edge (14mm thickness) of the board was marked with 5 markers at 5 inch intervals, the middle marker placed centrally on the front edge, to assist with reference when placing objects. A centrepiece of perspex, 51cm long, 5cm high and 10mm thick was glued to the centre of the board 6 inches from the front edge of the board. The front of the centre upright was marked with 10 markers at 2 inch intervals beginning 1inch from each end for convenience in placing the kidney beans.

APPENDIX 10

Jebsen Hand Test (pre-operative assessment form)

Dominance

Left	Right

NAME : .....
AGE : .....
POSITION OF PATIENT : .....
ASSESSMENT INTERVAL : .....
HAND BEING ASSESSED : .....

Time: .....

Date: .....

	FIRST ASSESSMENT			SECOND ASSESSMENT		
	Time	Pass/fail	Comments	Time	Pass/fail	Comments
Writing						
Cards						
Small Objects						
Simulated feeding						
Checkers						
Large Light Objects						
Large Light Objects						

APPENDIX 11

Jebsen Hand Test (post-operative form)

Dominance

Left	Right

NAME : .....
AGE : .....
POSITION OF PATIENT : .....
ASSESSMENT INTERVAL : .....
HAND BEING ASSESSED : .....

Time: .....

Date: .....

	FIRST ASSESSMENT			SECOND ASSESSMENT		
	Time	Pass/fail	Comments	Time	Pass/fail	Comments
Writing						
Cards						
Small Objects						
Simulated feeding						
Checkers						
Large Light Objects						
Large Light Objects						

APPENDIX 12

20th January 1997

Tel: 537-2414 W
556-1923 H

Dear Examiner,
Thank you for agreeing to be one of the examiners of tremor severity in patients with multiple sclerosis.

The tremor rating scale (TRS) was devised by Fahn originally for Parkinson's Disease patients and patients with essential tremor. It has not been validated in MS patients.

The patients in the Deep Brain Stimulation (DBS) study have a movement disorder resulting from MS namely ataxia and tremor affecting their upper limbs and/or trunk. The scale has therefore been modified very slightly for use on this group of patients.

The main reason for carrying out an inter-examiner reliability study is to determine the level of agreement between examiners in:

a) the subjective rating of tremor (Part A)
b) the spiral tests and pouring test (Part B)

I have enclosed the following:-

1) a video tape showing the standardised assessments of 10 patients
2) a copy of the video protocol
3) information on the TRS
    a) Guidelines
    b) Definitions of tremor
    c) Instructions for raters
4) Rating Scale Forms (one set for each patient A → J. Attached are copies of the patient's spiral drawings and handwriting).

Please read through the guidelines, definitions and instructions carefully before you begin.

I would be grateful if you could return the videotapes and completed TRS forms to me by Tuesday 4th February.

Many thanks in anticipation.

Yours sincerely,

Julie Hooper, Research Physiotherapist, DCN.

APPENDIX 13

RATER _____

PATIENT _____

TREMOR RATING SCALE TRS

PART A

1. Head tremor	0 = None		REST	☐
	1 = Slight. May be intermittent	POST		
	2 = Moderate amplitude. May be intermittent		ACT/INT	☐
	3 = Marked amplitude	GOAL		☐
	4 = Severe amplitude			
2. Trunk tremor	0 = None		REST	☐
	1 = Slight. May be intermittent	POST		
	2 = Moderate amplitude. May be intermittent		ACT/INT	☐
	3 = Marked amplitude	GOAL		☐
	4 = Severe amplitude			
3. Right Upper Extremity	0 = None		REST	☐
tremor	1 = Slight. May be intermittent		POST	a) ☐
	2 = Moderate amplitude. May be intermittent			b) ☐
	3 = Marked amplitude	ACT/INT		☐
	4 = Severe amplitude		GOAL	☐
4. Left Upper Extremity	0 = None		REST	☐
tremor	1 = Slight. May be intermittent		POST	a) ☐
	2 = Moderate amplitude. May be intermittent			b) ☐
	3 = Marked amplitude	ACT/INT		☐
	4 = Severe amplitude		GOAL	☐

PART B

5-6 Observe the patient joining both points of the spirals without crossing the lines and rate their drawings.

5. Drawing A
   Right

   Left

   0 = Normal

   1 = Slightly tremulous. May cross lines occasionally

   2 = Moderately tremulous or crosses lines frequently
   3 = Accomplishes the task with great difficulty. Many errors
   4 = Unable to complete drawing

6. Drawing B
   Right

   Left

   0 = Normal

   1 = Slightly tremulous. May cross lines occasionally

   2 = Moderately tremulous or crosses lines frequently
   3 = Accomplishes the task with great difficulty. Many errors
   4 = Unable to complete drawing

7. Pouring (use firm plastic cups, about 8cm tall, filled with water to 1cm from top. Ask patient to pour water from one cup to another. Test each hand separately).
   Right
   Left

   0 = Normal

   1 = More careful than a person without tremor, but no water is spilled
   2 = Spills a small amount of water (up to 10% of total amount)
   3 = Spills a considerable amount of water (> 10-50%)
   4 = Unable to pour water without spilling most of the water

APPENDIX 14

INSTRUCTIONS FOR RATERS

The video shows a standardised assessment of tremor being carried out on ten patients. The tape runs for 2 hours 45 mins in total. The patient is filmed carrying out the activities listed on the video protocol (see attached). The order of these activities may vary slightly.

The conversation between the researcher and the patients is included, i.e. the sound, as it makes the video tape more meaningful. However, examiners are free to agree or disagree with any comments made.

Assessments may not always appear to be straightforward. For example, it is difficult to assess postural tremor in the trunk if a patient is unable to maintain a posture or sit unsupported. However, please remember that one is assessing whether tremor is present and the degree to which it is occurring in a body part when the patient is attempting to achieve a certain position.

When a patient is moving a body part it is often difficult to differentiate between action tremor (occurring during the movement) and intention tremor (occurring at the end of the movement). They are therefore, grouped together for this reason.

When rating goal-related tremor please observe the video of the patient performing the spiral tests, the pouring test, the handwriting and card turning tests and rate the tremor in different parts of the body. Tremor may vary depending on the worst tremor observed when the patient performs these tasks.

Please watch the tape of all 10 patients (A → J). Starting at the beginning of the tape with patient A.

PART A -Whilst you watch the tape of each patient, rate their tremor (rest, postural, action/intention, goal related) for the:

- head
- trunk
- right upper limb
- left upper limb

Write a number (0 – 4) in the boxes provided.

PART B - Look at the photocopies of the patient's spiral drawings and hand writing (attached to the rating forms). Rate the spiral drawings and the pouring tests only, by writing a number in the appropriate box, as you observe them performing these tasks on the video.

Please read the guidelines and definitions of tremor before you begin and refer to these when making your judgements.

APPENDIX 15

FUNCTIONAL INDEPENDENCE MEASURE

UNIFORM DATA SYSTEM FOR MEDICAL REHABILITATION
FOLLOW-UP CODING SHEET Page 1 of 1

1. Facility Code
2. Patient Code

Follow-up Assessment

9. Admission Date (MONTH DAY YEAR)
11. Discharge Date (MONTH DAY YEAR)

29. Follow-up Date (MONTH DAY YEAR)

30. Follow-up Living Setting
1-Home 2-Board and Care 3-Transitional Living
4-Intermediate Care 5-Skilled Nursing Facility
6-Acute unit of own facility 7-Acute unit another facility
8-Chronic Hospital 9-Rehabilitation Facility 10-Other
11-Died 12-Alternate Level of Care

31. Follow-up Living With
(Complete only if item 30 is coded 1-Home.)
1-Alone 2-Family/Relatives 3-Friends
4-Attendant 5-Other

32. Follow-up Vocational Category
1-Employed 2-Sheltered 3-Student 4-Homemaker
5-Not Working 6-Retired-age 7-Retired-disability

33. Follow-up Vocational Effort
(Complete only if item 32 is coded 1,2,3 or 4.)
1-Full-time 2-Part-time 3-Adjusted workload

34. Follow-up Information Source
1-Patient 2-Family 3-Other

35. Follow-up Method
1-In person 2-Telephone 3-Mailed questionnaire

36. Follow-up Health Maintenance
1-Own care
2-Unpaid person or family
3-Paid attendant or aide
4-Paid, skilled professional
Primary
Secondary

37. Follow-up Therapy
1-None
2-Outpatient therapy
3-Home-based paid professional therapy
4-Both 2 and 3
5-Inpatient Hospital
6-Long-term Care Facility
7-Other

39. Functional Independence Measure (FIM)

38. Follow-Up Diagnoses (ICD-9 codes)
a. b. c. d. e. f. g.

		FOLLOW-UP
Self-Care		
A.	Eating	
B.	Grooming	
C.	Bathing	
D.	Dressing-Upper Body	
E.	Dressing-Lower Body	
F.	Toileting	
Sphincter Control		
G.	Bladder Management	
H.	Bowel Management	
Transfers		
I.	Bed, Chair, Wheelchair	
J.	Toilet	
K.	Tub, Shower	
Locomotion		
L.	Walk/Wheelchair	Walk / Wheelchair / Both
M.	Stairs	
Motor Subtotal Score		
Communication		
N.	Comprehension	Auditory / Visual / Both
O.	Expression	Vocal / Nonvocal / Both
Social Cognition		
P.	Social Interaction	
Q.	Problem Solving	
R.	Memory	
Cognitive Subtotal Score		
Total Motor and Cognitive Score		

FIM Levels

NO HELPER
7 Complete Independence (Timely, Safely)
6 Modified Independence (Device)

HELPER
Modified Dependence
5 Supervision
4 Minimal Assistance (Subject = 75 % +)
3 Moderate Assistance (Subject = 50 % +)
Complete Dependence
2 Maximal Assistance (Subject = 25 % +)
1 Total Assistance (Subject = 0 % +)

(NOTE: Leave no blanks; enter 1 if not testable due to risk)

APPENDIX 16

SITTING/STANDING/WALKING-STANDARDISED PROTOCOLS

NAME.....

DATE.....

ASSESSMENT INTERVAL.....

	TIME	PASS/FAIL
1 minute sitting balance		
10 second standing balance		
10 metre walk		

1. **1 minute 'static' sitting balance**
   A period of unsupported sitting without a back rest in excess of one minute. Hips, knees and ankles should be positioned at 90 degrees, with both feet flat on the floor. Independent sitting balance was defined as sitting unsupported on abed with head erect, eyes looking forward, trunk erect and not slumped with minimal flattening of the lumbar spine, thighs to remain in contact with the bed and no hand or arm support on bed. Weight should be distributed evenly between the ischial tuberositics and the head should adopt a midline position. The upper limbs should rest passively in the lap and should not resort to fixing with their hands.

2. **10 second standing balance**
   A period of unsupported standing in excess of 10 seconds. The weight should be evenly distributed between both feet in both coronal and sagital planes. Physical help is permissible in making the transition from sitting to standing, but during the timing period no help should be given.

3. **10 metre walk**
   A timed walk over a measured distance of 10 metres in a straight line using a hand-held stopwatch. The patient should commence the walk from a standing start, from a predetermined spot and be instructed to walk to a point distant to the end of the walkway. Timing should start at the beginning of the first step and finish as the patient crosses the mark indicating the end of the walkway. The assessor should walk beside the patient on the tremorous side both for reasons of security and to allow the most accurate judgement of the termination of the walking episode.

   Verbal instructions should be standardised to *"I would like you to walk to the far end of this room at a speed which is comfortable for you, but I will time how long it takes".*

   If appropriate a walking aid may be used but verbal cueing should be avoided.

APPENDIX 17

THE LONDON HANDICAP SCALE QUESTIONNAIRE

APPENDIX

Your health and your life

This questionnaire is about the way your health affects your everyday life. Please read the instructions for each question and then answer by ticking the box next to the sentence which describes you best.
When answering the questions, it may help to think about the things you have done over the last week and compare yourself with someone like you who is in good health

Mobility

Getting Around

Think about how you get from one place to another, using any help, aids or means of transport that you normally have available

1. DOES YOUR HEALTH STOP YOU FROM GETTING AROUND? *Please tick one box only* ☑

NOT AT ALL	You go everwhere you want to no matter how far away.	1
VERY SLIGHTLY	You go most places you want, but not all.	2
QUITE A LOT	You get out of the house, but not far away from it.	3
VERY MUCH	You don't go outside, but you can move around from room to room indoors	4
ALMOST COMPLETELY	You are confined to a single room, but you can move around in it	5
COMPLETELY	You are confined to a bed or a chair. You cannot move around at all. There is no-one to move you	6

Physical independence

Looking after yourself

Think about things like housework, shopping, looking after money, cooking, laundry, getting dressed, washing shaving and using the toilet

2. DOES YOUR HEALTH STOP YOU LOOKING AFTER YOURSELF? *Please tick one box only* ☑

NOT AT ALL	You do everything to look after yourself.	1
VERY SLIGHTLY	You need a little help now and again.	2
QUITE A LOT	You need help with some tasks (such as heavy housework or shopping) but no more than once a day	3
VERY MUCH	You do some things for yourself, but you need help more than once a day. You can be left alone safely for a few hours	4
ALMOST COMPLETELY	You need help to be available all the time. You cannot be left alone safely.	5
COMPLETELY	You need help with everything. You need constant attention, day and night	6

Occupation

Work and leisure

Think about things like work (paid or not), housework, gardening, sports, hobbies, going out with friends, travelling, reading looking after the children, watching television and going on holiday

3. DOES YOU HEALTH LIMIT YOUR WORK OR LEISURE ACTIVITIES? *Please tick one box only* ☑

NOT AT ALL	You do everything you want to do.	1
VERY SLIGHTLY	You do almost all the things you want to do.	2
QUITE A LOT	You find something to do almost all the time, but you cannot do some things for as long as you would like	3
VERY MUCH	You are unable to do a lot of things, but you can find something to do most of the time.	4
ALMOST COMPLETELY	You are unable to do most things, but you can find something to do some of the time.	5
COMPLETELY	You sit all day doing nothing. You cannot keep yourself busy or take part in any activities.	6

Social integration

Getting on with people

Think about family, friends and the people you might meet during a normal day

4. DOES YOUR HEALTH STOP YOU GETTING ON WITH PEOPLE? *Please tick one box only* ☑

NOT AT ALL	You get on well with people, see everyone you want to see, and meet new people	1
VERY SLIGHTLY	You get on well with people, but your social life is slightly limited	2
QUITE A LOT	You are fine with people you know well, but you feel uncomfortable with strangers	3
VERY MUCH	You are fine with people you know well, but you have few friends and little contact with neighbours. Dealing with strangers is very hard	4
ALMOST COMPLETELY	Apart from the people who look after you, you see no-one. You have no friends and no visitors	5
COMPLETELY	You don't get on with anyone, not even people who look after you	6

Orientation

Awareness of your surroundings

Think about taking in and understanding the world about you, and finding your way around in it *Please tick one box only*

5. DOES YOUR HEALTH STOP YOU UNDERSTANDING THE WORLD AROUND YOU? ☑

NOT AT ALL	You fully understand the world around you. You see, hear, speak and think clearly, and your memory is good	1
VERY SLIGHTLY	You have problems with hearing, speaking, seein or your memory, but these do not stop you doing most things	2
QUITE A LOT	You have problems with hearing, speaking, seeing or your memory, which make life difficult a lot of the time. But you understand what is going on.	3
VERY MUCH	You have (he/she has) great difficulty understanding what is going on	4
ALMOST COMPLETELY	He/she is unable to tell where he/she is or what day it is. He/she cannot look after him/herself at all	5
COMPLETELY	He/she is unconscious, completely unaware of anything going on around him/her	6

Economic self-sufficiency

Afford the things you need

Think about whether health problems have led to any extra expenses, or have cause you to earn less than you would if you were healthy

6. ARE YOU ABLE TO AFFORD THE THINGS YOU NEED? *Please tick one box only* ☑

YES, EASILY	You can afford everything you need. You have easily enough money to buy modern labour saving devices and anything you need because of ill health	1
FAIRLY EASILY	You have just about enough money. It is fairly easy to cope with expenses caused by ill health	2
JUST ABOUT	You are less well off than other people like you: however, with sacrifices you can get by without help	3
NOT REALLY	You only have enough money to meet your basic needs. You are dependent on state benefits for extra expenses	4
NO	You are dependent on state benefits, or money from other people or charities. You cannot afford the things you need	5
ABSOLUTELY NOT	You have no money at all and no state benefits. You are totally dependent on charity for your most basic needs	6

APPENDIX 18

SPSS PROGRAMME FOR CALCULATING OVERALL LONDON HANDICAP SCORE

Box: SPSS programme for calculating overall handicap score

```
get/file = 'c:\....\lhs.sav'.

title "LONDON HANDICAP SCALE".

if (mobil =1) um = 6.8.
if (mobil =2) um = 2.5.
if (mobil =3) um = -0.3.
if (mobil =4) um = -3.2.
if (mobil =5) um = -6.1.
if (mobil =6) um = -9.0.

if (occup =1) uoc = 6.5.
if (occup =2) uoc = 1.1.
if (occup =3) uoc = 0.4.
if (occup =4) uoc = -0.2.
if (occup =5) uoc = -0.9.
if (occup =6) uoc = -6.8.

if (physind =1) upi = 9.6.
if (physind =2) upi = 0.8.
if (physind =3) upi = -0.7.
if (physind =4) upi = -2.2.
if (physind =5) upi = -5.2.
if (physind =6) upi = -8.2.

if (social =1) usi = 8.0.
if (social =2) usi = 5.3.
if (social =3) usi = 2.4.
if (social =4) usi = -1.0.
if (social =5) usi = -3.7.
if (social =6) usi = -6.8.

if (orient =1) uor = 9.4.
if (orient =2) uor = 1.8.
if (orient =3) uor = -3.4.
if (orient =4) uor = -5.8.
if (orient =5) uor = -7.7.
if (orient =6) uor = -9.8.

if (econ =1) uess = 9.2.
if (econ =2) uess = 6.1.
if (econ =3) uess = 2.9.
if (econ =4) uess = -2.2.
if (econ =5) uess = -6.1.
if (econ =6) uess = -9.9.

compute lhs = 50.5+um+uoc+upi+usi+uor+uess.
VARIABLE LABELS lhs 'handicap score'.
```

APPENDIX 19

NAME .....

DATE .....

ASSESSMENT INTERVAL .....

Assessment of Handicap self- questionnaire

Please answer the following questions by putting a circle around the appropriate letter.

Has your tremor stopped you

1. working?	A	B	C	D
2. applying for a job or promotion?	A	B	C	D
3. shopping by yourself ?	A	B	C	D
4. doing a favourite hobby or sport ?	A	B	C	D
5. travelling by public transport?	A	B	C	D
6. driving a car?	A	B	C	D
7. eating out?	A	B	C	D
8. going on holiday?	A	B	C	D
9. accepting a party invitation?	A	B	C	D

Key :

- A no
- B yes because you are embarrassed by the tremor
- C yes because of the physical difficulties produced by the tremor
- D yes because of both the physical difficulties and the embarrassment produced by the tremor

APPENDIX 20

Hospital Anxiety and Depression Scale (HADS)

NFER NELSON

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		
2		A lot of the time		
1		From time to time, occasionally		
0		Not at all		
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		

This form is printed in green. Any other colour is an unauthorized photocopy.

Code 4460 01 4 Printed in Great Britain

APPENDIX 21

NAME: .....

DATE: .....

ASSESSMENT INTERVAL .....

FATIGUE SEVERITY SCALE

1. My motivation is lower when I am fatigued.

Choose a number from 1 to 7 that indicates your degree of agreement with this statement and mark it on the line below.

Strongly disagree _____ Strongly agree

1 2 3 4 5 6 7

2. Exercise brings on my fatigue.

Choose a number from 1 to 7 that indicates your degree of agreement with this statement and mark it on the line below.

Strongly disagree _____ Strongly agree

1 2 3 4 5 6 7

3. I am easily tired.

Choose a number from 1 to 7 that indicates your degree of agreement with this statement and mark it on the line below.

Strongly disagree _____ Strongly agree

1 2 3 4 5 6 7

4. Fatigue interferes with my physical functioning.

Choose a number from 1 to 7 that indicates your degree of agreement with this statement and mark it on the line below.

Strongly disagree _____ Strongly agree

1 2 3 4 5 6 7

5. Fatigue causes frequent problems for me.

Choose a number from 1 to 7 that indicates your degree of agreement with this statement and mark it on the line below.

Strongly disagree _____ Strongly agree

1 2 3 4 5 6 7

6. My fatigue prevents sustained physical functioning.

Choose a number from 1 to 7 that indicates your degree of agreement with this statement and mark it on the line below.

Strongly disagree _____ Strongly agree

1 2 3 4 5 6 7

7. Fatigue interferes with carrying out certain duties and responsibilities.

Choose a number from 1 to 7 that indicates your degree of agreement with this statement and mark it on the line below.

Strongly disagree _____ Strongly agree

1 2 3 4 5 6 7

8. Fatigue is among my three most disabling symptoms.

Choose a number from 1 to 7 that indicates your degree of agreement with this statement and mark it on the line below.

Strongly disagree _____ Strongly agree

1 2 3 4 5 6 7

9. Fatigue interferes with my work, family, or social life.

Choose a number from 1 to 7 that indicates your degree of agreement with this statement and mark it on the line below.

Strongly disagree _____ Strongly agree

1 2 3 4 5 6 7

APPENDIX 22

Patient's name.....

Date.....

Assessment interval.....

PATIENT'S OPINION OF THE OPERATION

Please give us your opinion of how you feel about the operation.

Are you:-

Enthusiastic

Satisfied

Moderately positive

Negative

about the outcome.

Please circle the appropriate description of how you feel.

APPENDIX 23

DETAILED PATIENT INFORMATION SHEET ABOUT STUDY OF THALAMIC STIMULATION FOR MOVEMENT DISORDERS IN MULTIPLE SCLEROSIS.

You are being asked to participate in a research study to demonstrate the safety, reliability, and effectiveness of deep brain stimulation (DBS) for the suppression of movement disorders caused by Multiple Sclerosis. If you choose to participate, you will be one of 15 individuals participating in this clinical investigation and the duration of your participation is expected to last 12 months. The following document briefly describes the device to be used and possible complications which might occur.

BACKGROUND

Electrical stimulation has been used for over 20 years to treat hundreds of patients suffering from chronic pain. Recent European studies have shown that DBS may suppress tremor associated with Parkinson's disease and essential tremor when an area of the brain called the VIM of the thalamus is stimulated. A destructive lesion, or thalamotomy, of this area can also control tremor, but may have permanent side effects. The effectiveness and safety of deep brain stimulation for controlling tremor in patients with MS. is currently not known.

The DBS system consists of:

*a lead which consists of insulated wires with four electrodes at the end.
*an extension wire which connects the lead to the power source
*an Implanted Pulse Generator (IPG) which is the power source

The IPG is a metal "can" about two inches in diameter and about 1/2 inch thick. It contains a small battery and produces the electrical pulses needed for stimulation. The battery cannot be replaced without replacing the entire IPG. Replacing the IPG involves minor surgery. Battery life varies for each patient depending on the type and intensity of stimulation needed for good tremor relief. For patients using DBS to treat chronic pain, battery life has been typically been three to five years.

IMPLANTATION PROCEDURES

The implantation usually takes place in two stages. During the first stage you will have an MRI or CT Scan to determine the proper location for the lead within you our brain. The leads are then carefully placed in the brain using a procedure called stereotactic neurosurgery. This procedure has been used in brain surgery for movement disorders such as Parkinson's disease and multiple sclerosis for at least 40

years. The lead is implanted through a small opening (l/2 inch) in the skull using local anaesthetic and mild sedation. A small area of your hair must be shaved to avoid the risk of serious contamination from bacteria.

During the procedure your doctor may ask a number of questions about what you feel and how your tremor feels. He is doing this to make sure the lead is in exactly the right place in the brain. Your doctor will test the DBS system to see if your tremor is reduced adequately. The lead may be connected to wires which run through the skin to a temporary external stimulator.
If you receive good tremor relief, that is sustained over a few days the second stage of the implantation takes place. During the second stage, a permanent extension wire is passed under the skin of the neck and attached to the IPG. The IPG is also placed under the skin, usually just below the collar bone.

If you do not receive adequate relief of tremor, you will **not** have the complete DBS System implanted. In this case, you will return to your physician at one month and six months for follow-up assessments.

BENEFITS

You may gain substantial control over your medically refractory movement disorder due to multiple sclerosis.
This may improve your quality of life and allow you to participate more fully in some activities of daily living.

The ITREL* II IPG is programmable and permits you and the researcher to choose the parameters which provide maximum relief with minimal side effects. The researcher can adjust the stimulation many different ways to provide you with the best comfort and tremor relief. In addition y our will be provided with a magnet so you can turn the stimulation off and on.

RISKS

Every effort is made to minimise the risks of the surgery and of brain stimulation, however, complications may occur. Besides the general surgery and anaesthesia risks your doctor has explained to you, the following complications due to implantation of this device may occur:

- Bleeding (haemorrhage) inside the brain, which could lead to a stroke, causing severe neurological damage, such as weakness, paralysis, or speech problems, or even death. The risk of stroke increases with age. If you have high blood pressure or are over 60 years old, the risk is about 5%. If you are under 40 the risk is about 1%.

Much less common complications include:

- Weakness of movement, double vision or other vision problems, loss of sensation or mental impairment.

- Infection, in which case the lead may need to be removed and/or antibiotic therapy may be necessary. Some infections, such as meningitis and brain abscesses, may be serious enough to cause death.

- Seizures

- Leaking of the fluid which surrounds the brain.

Problems which occur after the lead and IPG are implanted

- Mechanical or electrical problems, leading to failure of the DBS system. For example the lead or extension wires may fracture or components may need to be replaced. This may require further surgery.

- Persistent pain or fluid accumulation (seroma) at the IPG site for around the system components. The components may change position or erode through the skin, leading to infection and scarring. This may necessitate removal of the DBS system

- Allergic reaction or rejection of the implanted system

- Migration of movement of the lead out of the brain.

Problems which may occur with stimulation

- Effectiveness or comfort of stimulation changing over time.

- Persistent paraesthesia (tingling) in the limbs or in the face.

- Speech problems, such as dysphasia (loss of ability to use or understand language) or dysarthria (difficulty in speaking words)

- Disequilibrium (dizziness/light headedness)

- Movement problems such as dyspraxia (incoordination), dystonia (altered muscle tone) facial and limb muscle weakness or partial paralysis and abnormal voluntary movements.

- Paraesthesis (decreased sensory ability or numbness)

- Attention and cognitive deficits.

- Temporary worsening of the tremor when stimulation is stopped or "rebound"

- Most of the stimulation side effects can be avoided by reprogramming the IPG or turning the IPGH off. Other side effects or complications may occur which are more unusual or are not yet known and cannot be predicted at this time.

METHODS TO MINIMISE RISKS

Your doctor will ask for your medical history, and you will have a full physical and neurological examination to determine if it is appropriate for you to participate in this DBS study. To reduce the risks during surgery, careful surgical and sterile operating methods are used. All the parts of the system are carefully manufactured and the implantable parts are supplied sterile. The neurological risks are reduced by careful lead placement for proper location and avoiding critical areas of the brain.

Test stimulation may determine if there are any undesirable side effects from the stimulation. If there are undesirable side effects, the system can be removed. After surgery, regular visits to y our doctor will help to detect any complications with the system and allow treatment to begin as soon as possible. Many side effects and complications can be avoided or treated by reprogramming parameters of stimulation or discontinuing stimulation. You may have to compromise between side effects and tremor control.

You should contact your physician if you incur any injuries, complications, or adverse effects associated with this therapy.

ALTERNATIVES

The main alternative therapy is thalamotomy, which is a destructive lesion in the brain. Your physician can explain the risk and benefits associated with this type of therapy.

RIGHTS TO INFORMATION AND CONFIDENTIALITY

Your involvement in this study is confidential and y our rights are protected by national and local laws. You will not be identified by name in any published reports about this study, however, the records of this study may be inspected by your doctor and hospital.

CHOOSING TO PARTICIPATE

Participation in this study is entirely up to you. You may refuse to participate or may choose to stop participating at any time without penalty or loss of benefits you would normally be entitled to without the study. If you choose not to participate, your doctor will provide information on any other procedures that might help you instead.

If you choose to participate in the study, you will need to return to this study centre for several follow-up visits (at one, three, six and l2 months). You will be required to

help the researcher complete a number of questionnaires concerning your DBS for tremor treatment both before and after the surgery. You will also be required to be videotaped a number of times with y our stimulator ON and OFF to measure the results of your stimulation. You will not receive any payment for participation in this study.

The DBS system is considered by your doctor to be of potential benefit for relieving your tremor. Your doctor knows about the risks of implanting this DBS system and has determined that the benefits which you may get from the implant outweigh the risks.

APPENDIX 24

Does Thalamic Stimulation Decrease Tremor Associated with Multiple Sclerosis

CONSENT FORM

Patient's Name:.....

Have you read the information sheet?	Yes / No
Have you asked further questions about the study?	Yes / No
Who has explained the study to you?	.....
Have you had sufficient time to consider your reply?	Yes / No
Do you agree to take part?	Yes / No
Are you aware that you can ask to withdraw from the study at any time, without needing to give a reason, and with no effect on your care in other respects?	Yes / No
Have you been told that impartial advice is available if you are still concerned about participating?	Yes / No

If you are willing take part, please sign,

Signature ..... Date .....

Signature of Investigator ..... Date .....

Copies:
1) Investigator
2) To be retained by patient/subject
3) To patients GP
4) File case notes

APPENDIX 25

CONSENT FORM

1. Videotaking of assessment sessions

I agree to be assessed by a Physiotherapist using some simple tests. I understand that these tests are being evaluated for use in a research project for patients with Multiple Sclerosis. I agree to the use of videotaping equipment during the assessment sessions. I give my consent for the videotape of me to be studied by medical staff involved in the research project evaluating the effect of thalamic deep brain stimulation on movement disorders in multiple sclerosis.

I am aware that I can withdraw my consent at any time during the assessment and that the information will be used for research purposes only.

Signed.....

Dated.....

2. The use of videotapes for teaching session

I give my consent for the videotape of me to be used for the teaching and education of staff and students in medical, paramedical and nursing professions. I am aware that I can withdraw consent for the use of the videotape for teaching purposes at any time, either during testing or at a later date.

Signed.....

APPENDIX 26

THALAMIC STIMULATION FOR THE TREATMENT OF TREMOR

ENTRY NOTE

Please print or type **Form 1**

1. Patient Identifier _____ _____ _____

2. Date of Birth _____ / _____ / _____
   month day year

3. Neurologist _____

4. Date of Evaluation _____ / _____ / _____

5. Has patient provided signed informed consent?	☐ Yes	☐ No Stop*
6. Has patient been diagnosed with Multiple Sclerosis where tremor constitutes a significant function disability?	☐ Yes	☐ No Stop*
7. Has tremor been consistently disabling in the target extremity for at least three months prior to enrolment?	☐ Yes	☐ No Stop*
8. Is patient available for follow-up for the duration of the study?	☐ Yes	☐ No Stop*
9. If patient has Multiple Sclerosis, have medications been held constant for at least 1 month prior to enrolment?	☐ Yes	☐ No Stop*
10. If patient has Multiple Sclerosis, are fluctuations predictable?	☐ Yes	☐ No Stop*
11. Is patient a surgical candidate?	☐ Yes	☐ No Stop*
12. Is patient between the ages of 18 and 80 years old, inclusive?	☐ Yes	☐ No Stop*
13. Was tremor adequately controlled by medications during the 3 months prior to enrolment?	☐ Yes Stop*	☐ No
14. Has patient undergone a thalamotomy procedure?	☐ Yes	☐ No
15. Does patient have other clinically or medically significant disease?	☐ Yes	☐ No
16. Does patient have a history of dementia that would interfere with the ability to participate in this study?	☐ Yes	☐ No
17. Does patient have history of alcohol or drug abuse?	☐ Yes	☐ No

*Do **NOT** Enrol Patient

INVESTIGATOR SIGNATURE_____ DATE_____

APPENDIX 27

DEEP BRAIN STIMULATION STUDY

PATIENT ASSESSMENT RANDOMISATION SHEET

PATIENT 1

ASSESSMENT: 1 MONTH

Your Name .....

Patient's Name.....

Date of Assessment.....

Thank you for agreeing to help with this study, which involves two functional assessments of the patient, one with the stimulator switched on, the other with it off. So that we can remove learning and fatigue effects, we would like to have some patients perform the assessments in the order Off-ON, and some in the order ON-OFF. Also, in order to allow an objective assessment of the effectiveness of the stimulator, the assessor (Julie Hooper) should not know whether or not the devise is switched on. Please could you ensure that the stimulator is set to the correct operation for each assessment, as given below, without telling Julie Hooper which state the patient is in.

First Assessment	**Stimulator OFF**
Second Assessment	**Stimulator ON**

After setting the stimulator for the second assessment period, please put this sheet of paper into the envelope provided, seal it, and give it to Julie Hooper.

Thank you very much for your help.

APPENDIX 28

Turning the stimulator on/off using the console

1. Hold the console programming head over the patient's scar (under their clavicle).

2.Press the REVIEW key on the programming head.

3.Then look at the top row of parameters on the console. Read along until you come to IPG output. Does it say on or off? What setting do you want?
- if it's set on the setting that you want then leave things as they are and turn the console off.

- if you want to change it to the opposite mode then :-
a) first press the IPG output button on the programming console.
b) then press EITHER the orange ON or the orange OFF switch on the console.
c) THEN PRESS THE PROGRAM KEY ON THE PROGRAMMING HEAD SO THAT THE STIMULATOR IS CHANGED TO THE APPROPRIATE MODE.

4. To double check that the stimulator is set on the correct mode look along the top row of programmable parameters on the console until you come to IPG output and this should confirm the mode that you have set the stimulator to.

PLEASE NOTE
It is very important that the stimulator is set to the correct on or off setting as stated in the sealed envelope and that the research physiotherapist is not aware of these settings. If you have any difficulties in setting the stimulator to the desired mode please ask the research physiotherapist to show you how to set the stimulator again.

APPENDIX 29

THALAMIC STIMULATION FOR THE TREATMENT OF TREMOR

Please print or type **LEAD IMPLANT** **Form 3**

1. Patient Identifier _____ _____ _____

2. Date of Birth _____ / _____ / _____
   month day year

3. Neurologist _____

4. Neurosurgeon _____

5. Date of Procedure _____ / _____ / _____
   month day year

6. Lot Number of Lead: ____ ____ ____ ____ ____ ____

7. Target VIM: ☐ Left ☐ Right

8. Target Extremity: ☐ LUE ☐ RUE
   ☐ LLE ☐ RLE

9. Technique for target localization PRIOR to lead implant (check all that apply):
   ☐ Ventriculography ☐ CT ☐ MRI ☐ Other,specify_____

10. Stereotactic frame used:
    ☐ Leksell ☐ CRW ☐ BRW ☐ Other,specify_____

11. How many times was a mapping electrode passed?_____

12. Optimum effect stimulating with mapping electrode
    ☐ No suppression of tremor
    ☐ Mild suppression of tremor
    ☐ Moderate suppression of tremor
    ☐ Complete suppression of tremor

13. Optimum effect stimulating with 3382 DBS Lead:
    ☐ No suppression of tremor
    ☐ Mild suppression of tremor
    ☐ Moderate suppression of tremor
    ☐ Complete suppression of tremor

14. Optimum effect WITHOUT stimulating with 3382 DBS Lead:
    ☐ No suppression of tremor
    ☐ Mild suppression of tremor
    ☐ Moderate suppression of tremor
    ☐ Complete suppression of tremor

15. Device used for electrical stimuation: ☐ Medtronic Model 3625 Screener ☐ Other,specify_____

16. Was the 3382 DBS Lead implanted? ☐ Yes ☐ No
    If No, why wasn't the lead implanted? ☐ No tremor suppression ☐ Other,specify_____

17. Technique for target verification AFTER lead placement (check all that apply):
    ☐ Ventriculography ☐ CT ☐ X-ray ☐ Other,specify_____

18. Final 3382 DBS Lead coordinates (0-electrode in relation to AC-PC line):
    ____mm lateral to AC-PC Line; ____mm from PC along AC-PC Line;____mm above (+) or below (-) AC-PC Line

19. Was the 3382 DBS Lead implanted in the longitudinal axis of VIM? ☐ Yes ☐ No

20. Were there complications during lead implant: ☐ Yes ☐ No
    If yes, complete Complication Form 7 or 8

INVESTIGATOR SIGNATURE_____ DATE_____

APPENDIX 30

THALAMIC STIMULATION FOR THE TREATMENT OF TREMOR

IPG INTERNALISATION

Please print or type **Form 4**

1. Patient Identifier _____ _____ _____

2. Date of Birth _____ / _____ / _____
   month day year

3. Neurologist _____

4. Neurosurgeon _____

5. Date of IPG internalisation procedure: _____ / _____ / _____

6. Was the IPG internalised?

   ☐ Yes ☐ No

7. Were there any complications during IPG internalisation?

   ☐ Yes ☐ No

   If yes, complete Complication Form 7 or 8.

8. Location of Itrel®II IPG: ☐ Left subclavicular pocket
   ☐ Rich subclavicular pocket
   ☐ Other,specify _____

9. Location of connector: ☐ Head ☐ Neck ☐ Other,specify_____

10. Serial numbger of Itrel®II IPG: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

11. Serial number of extension ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

12. Length of extension cable: _____ cm

INVESTIGATOR SIGNATURE _____ DATE _____

APPENDIX 31

THALAMIC STIMULATION FOR THE TREATMENT OF TREMOR

STIMULATION (IPG) PARAMETERS

Please print or type **Form 5**

1. Patient Identifier _____ _____ _____

2. Date of Birth _____ / _____ / _____
   month day year

3. Neurologist _____

4. Date of evaluation _____ / _____ / _____
   month day year

5. Assessment Interval: ☐ Discharge ☐ 6 month ☐ Other,specify:_____
   ☐ 1 month ☐ 9 month
   ☐ 3 month ☐ 12 month

6. Stimulation (PG) parameters at beginning of visit: (Attach printcut from console programmer)

   Amplitude: _____ Volts

   Rate: _____ Hz

   Pulse Width: _____ µsecs

   Impedance: 0-EL _____ Ohms
   1-EL _____ Ohms
   2-EL _____ Ohms
   3-EL _____ Ohms

7. Stimulation (IPG) parameters at end of visit: (Attach printout from console programmer)

   Amplitude: _____ Volts

   Rate: _____ Hz

   Pulse Width: _____ µsecs

   Impedance: 0-EL _____ Ohms
   1-EL _____ Ohms
   2-EL _____ Ohms
   3-EL _____ Ohms

8. Instructions for patient to:

   _____ Continuously stimulate
   _____ Turn OFF at night
   _____ Use as needed
   _____ Other, specify: _____

If any current complications or side effects, or any since last follow-up visit, complete Form 7 and/or 8.

INVESTIGATOR SIGNATURE _____ DATE _____

APPENDIX 32

Information about Jacqueline's stimulator

Jacqueline has a rectangular shaped stimulator implanted under the skin on the left side of her chest under the collar bone (she has a 3inch scar over the stimulator site). The stimulator needs to be turned on in the morning and off at night to conserve the battery. Jacqueline may find this difficult to do particularly if her stimulator is switched off as one needs a fairly steady hand. The stimulator is turned on and off by holding a small blue magnet over the stimulator for 2 seconds, which effectively works like a switch. It is possible to check whether or not the stimulator has been turned on or off successfully with the magnet by holding a transistor radio over the stimulator. The radio should be tuned on AM and should be set at the lower end of the waveband at 530 KHz and turned on. If the stimulator is on you will hear a buzzing/ interference sound when you hold the radio over the stimulator. If it is off you will only hear the faint hissing noise of the volume.

How to turn Jacqueline's stimulator on/off

1. Stand on Jacqueline's left hand side. Hold the blue magnet in your left hand and palpate the stimulator box in Jacqueline's chest with your right hand.

2. Hold the magnet at arms length and bring the magnet in on top of the stimulator holding it horizontally. Hold it there for 2 seconds and then remove it. This should switch the stimulator either on or off depending on what mode it was in when you started.

3. To check which mode it is in **USE THE RADIO**.
Turn it on and turn the volume control up until you can hear a faint hissing sound coming from the radio. Hold the radio with the wavelength band facing upwards and over Jaqueline's stimulator. You should hear some buzzing/interference if it is on and only the hissing sound of the volume if it is off. You may have to move it very slightly around the stimulator area.

Any problems please contact the research physiotherapist-Mrs Julie Hooper on 0131 537 2414 (work- mornings only) or at home on 0131 556 1923 (ansa phone)

APPENDIX 33

THALAMIC STIMULATION FOR THE TREATMENT OF TREMOR

FOLLOW-UP

Please print or type **Form 6**

1. Patient Identifier _____ _____ _____

2. Date of Birth _____ / _____ / _____
   month day year

3. Neurologist _____

4. Date of evaluation _____ / _____ / _____
   month day year

5. Follow-up Internal: ☐ 1 month ☐ 6 month ☐ 12 month
   ☐ 3 month ☐ 9 month ☐ Other, specify: _____

6. Device Status: ☐ In Use ☐ Stimulation Discontinued, complete Adverse Event Form 7 or Complication Form 8.

7 Have any components been explanted since last follow-up?

☐ YES, complete Complication Form 8. ☐ NO

8. Have there been any side effects or complications since last follow-up?

☐ YES, complete Adverse Event Form 7 or Complication Form 8. ☐ NO

9. Stimulator use since last follow-up:

a. Use: ☐ Day Only ☐ Night Only ☐ Night and Day ☐ Not Used
b. Pattern: ☐ Continuously ☐ Intermittently, as needed ☐ Not Used

10. Average number of hours per day stimulation is on: _____ Hours

11. When stimulation is turned off, does tremor amplitude appear to decrease over time before stabilising? ☐ Yes ☐ No

If YES, enter the number of minutes from the time the stimulator is turned off until tremor stabilises: _____ Minutes

12. Instructions to patient regarding future use:

a. Use: ☐ Day Only ☐ Night Only ☐ Night and Day ☐ Not Used
b. Pattern: ☐ Continuously ☐ Intermittently, as needed ☐ Not Used

INVESTIGATOR SIGNATURE _____ DATE _____

APPENDIX 34

THALAMIC STIMULLATOR FOR THE TREATMENT OF TREMOR

THERAPY ADVERSE EVENTS

Please print or type **Form 7**

1. Patient Identifier _____ _____ _____

2. Date of Birth _____ / _____ / _____
   month day year

3. Neurologist _____

4. Date of evaluation _____ / _____ / _____
   month day year

5. Date of event: _____ / _____ / _____
   month day year

6. Enter appropriate codes from the lists below (complete a separate form for each event).

   Adverse Event: _____ Severity: _____ Status: _____ Date Resolved: _____ / _____ / _____
   month day year

   Etiology: _____ Casualty:_____ Interventions: _____. _____ . _____

   Relationship to Stimulation: _____

REPORT DEATH ON FORM # 16: STUDY TERMINATION

Adverse Event:
1. Paresis; Extremity Weakness
2. Paralysis
3. Double Vision
4. Headaches
5. Eye Movement Disorders
6. Dysphasia
7. Dysarthria
8. Disequilibrium
9. Facial Weakness
10. Seizures
11. Dyspraxia
12. Dystonia
13. Dyskinesia
14. Attention or Cognitive Deficits
15. Sensory Deficits
16. Gait Disorders
17. Rebound
18. Intracranial haemorrhage
19. Paresthesia
20. Death
21. System Complications (Complete Form 8)
22. Other, specify:_____ _____

Severity:
1. Mild
2. Moderate
3. Serious

Etiology:
1. Stimulation
2. Concomitant Drugs
3. Disease Progression
4. System Components
5. Patient Related Condition
6. Unknown
7. Other, specify: _____ _____ _____

Interventions:
1. No Intervention
2. Patient Education
3. Stimulation Parameters Changed
4. Stimulation Discontinued
5. Concomitant Drug Reduced
6. Concomitant Drug Discontinued
7. Components Explanted (Complete Complication Form 8)
8. Other, specify: _____

Status:
1. Resolved
2. Ongoing

Casualty of Etiology to Event:
1. Remote
2. Possible
3. Probable
4. Definite

Relationship to Stimulation:
1. Present Only with Stimulation
2. Present Only without Stimulation
3. Present Both with and without Stimulation

INVESTIGATOR SIGNATURE _____ DATE _____

APPENDIX 35

THALAMIC STIMULATION FOR THE TREATMENT OF TREMOR

SYSTEM COMPLICATIONS

Please print or type **Form 8**

1. Patient Identifier _____ _____ _____

2. Date of Birth _____ / _____ / _____
   month day year

3. Neurologist _____

4. Date of evaluation _____ / _____ / _____
   month day year

5. Date of Complication _____ / _____ / _____
   month day year

6. Enter appropriate codes from the lists below (complete a separate form for each complication).

   Complication: _____ Severity: _____ Status: _____ Date Resolved: _____ / _____ / _____
   month day year

   Etiology: _____ Casualty: _____ Interventions: _____ . _____ . _____

REPORT DEATH ON FORM # 16: STUDY TERMINATION

System Complications:
1. Seroma
2. Hematoma
3. Erosion
4. Infection
5. CSF Leak
6. Intracranial Haemorrhage
7. No Stimulation
8. Intermittent Stimulation
9. Loss of Effect
10. Lead Migration
11. Lead Dislodgement
12. Lead Fracture
13. Burr Hole Ring & Cap Failure
14. IPG Malfunction
15. Extension Fracture
16. Extension Malfunction
17. Telemetry Failure
18. Programmer Malfunction
19. Printer Malfunction
20. Therapy Side Effects (Complete Form 7)
21. Other, specify: _____

Severity:
1. Mild
2. Moderate
3. Serious

Status:
1. Resolved
2. Ongoing

Etiology:
1. Lead
2. IPG
3. Extension
4. Burr Hole Ring & Cap
5. IPG-Extension Connection
6. Lead-Extension Connection
7. Surgical Procedure
8. Patient Related Condition
9. Patient Activity
10. Physician/Staff Related
11. Unknown
12. Other, specify: _____

Casualty of Etiology to Complication:
1. Remote
2. Possible
3. Probable
4. Definite
5. Unknown

Interventions:
1. No intervention
2. Patient Education
3. Lead Explanted
4. Lead Repositioned
5. Lead Replaced
6. Burr Hole Ring & Cap Replaced
7. Burr Hole Ring & Cap Repositioned
8. Extension Explanted
9. Extension Replaced
10. IPG Explanted
11. IPG Replaced
12. IPG Reprogrammed
13. Aspiration
14. Antibiotic Therapy
15. Local Therapy
16. Programmer Replaced/Repaired
17. Surgical Exploration/ Local Anaesthetic
18. Surgical Exploration/ General Anaesthetic
19. Other, specify: _____

INVESTIGATOR SIGNATURE _____ DATE _____

APPENDIX 36

Patient's name.....

Date.....

Assessment interval.....

	ON	OFF
Is the patient able to turn the stimulator		

APPENDIX 37

Table showing descriptive data of the total tremor scores for the target arm

The components of tremor (postural a), postural b), kinetic/intention and goal-related) were scored on a 5 point scale (0 – 4), with a higher score indicating increased severity of tremor. The scores for the different components were summed to give a total tremor score for the target arm (best possible score = 0, worst possible score = 16).

Time of Assessment		Total Tremor Score				
	N	Median	Mean	S.D.	Minimum	Maximum
Pre-op	12	12	11.5	2.35	7	15
1 month OFF	11	7	7.36	4.37	1	15
1 month ON	9	5	4.56	1.81	2	8
3 months OFF	8	8.5	9.38	4.24	4	16
3 months ON	8	5.5	5.50	2.20	3	9
6 months OFF	9	8	8.22	4.52	2	16
6 months ON	9	5	6.44	4.13	2	16
12 months OFF	8	9	9.13	4.02	3	16
12 months ON	7	5	5.14	2.41	3	10

APPENDIX 38

Table showing descriptive data of the total number of successful Jebsen subtests with the target arm

The Jebsen Test of Hand Function included 7 subtests of upper limb performance. The test was scored by counting the number of successful subtests performed by the patient: allocating 1 for a pass and 0 for a fail. The higher the score the better the performance on the subtests (best score = 7, worst score = 0).

Time of Assessment		Total number of successful Jebsen subtests				
	N	Median	Mean	S.D.	Minimum	Maximum
Pre-op	12	1.5	1.33	0.98	0	3
1 month OFF	11	2	2.82	1.72	1	6
1 month ON	9	5		1.56	2	7
3 months OFF	8	1.5	3	2.56	1	7
3 months ON	8	4.5	4.5	2.33	2	7
6 months OFF	9	2	2.67	2.65	0	7
6 months ON	9	4	3.67	2.45	0	7
12 months OFF	8	2	2.50	2.45	0	7
12 months ON	7	5	4.43	2.15	1	7

APPENDIX 39

Video to supplement written work of thesis showing patients with movement disorders due to MS in whom thalamic DBS were implanted in the study

The video shows clips of patients being assessed using the Modified Fahn's Tremor Rating Scale to rate severity of tremor amplitude and the Jebsen Test of Hand Function to measure the successful performance of Jebsen subtests with the target arm. It shows patients in whom the movement disorder predominately affects the upper limbs and patients in whom the movement disorder affects the head, and the trunk as well as the upper limbs.

One patient is shown demonstrating a beneficial microthalamotomy effect after the operation, the beneficial symptomatic and functional effect of thalamic DBS 12 months after operation can be seen in 2 patients. The last patient shown on the video demonstrates the functional limitations in performing activities of daily living after the operation due to the persistence of intention tremor and dysmetria.

APPENDIX 40

PUBLISHED WORK

Whittle IR, Hooper J, Mumford C, Pentland B., Taylor R. Derivation of a test battery to evaluate the effects of thalamic DBS in patients with MS. **Acta Neurochir (Wien)** 138; 644-5, 1996.

Hooper J, Mumford C, Pentland B, Signorini D, Taylor R, Whittle IR. Validation of a tremor rating scale to determine effects of thalamic deep brain stimulation for movement disorders in patients with multiple sclerosis. **J Neurol Neurosurg Psychiat** 63; 130, 1997.

Hooper J, Taylor,R, Pentland B, Whittle IR. Rater reliability of Fahn's Tremor Rating Scale in patients with multiple sclerosis. ***Arch Phys Med Rehabil*** 79; 1076-1079, 1998.

Whittle IR, Hooper J, Pentland B. Thalamic deep brain stimulation for movement disorders in multiple sclerosis. ***Lancet*** 351; 109-110, 1998.

Hooper J, Whittle IR. Long-term outcome after thalamotomy for movement disorders in multiple sclerosis. ***Lancet*** 352; 1984, 1998.

Hooper J, Pentland B, Whittle IR. Problems associated with thalamic deep brain stimulation for movement disorders due to multiple sclerosis. **Multiple Sclerosis** 4 (Supp 1);S7, 1998.

Whittle IR, Hooper J. Thalamic DBS for non-Parkinsonian movement disorders. ***Brit J Neurosurg*** 13; 539, 1999

Yau Y-H, Hooper J, Whittle IR. Long term outcome following thalamotomy for movement disorders. **Brit J Neurosurg** 13; 539, 1999

and in-vitro immune function, and immunity against opportunistic infections in complete DGA. Potential future uses of lymphocyte transplantation may include immune constitution of children with other T-cell deficiencies, as well as of functionally athymic adults after bone-marrow transplants.

1 Ammann AJ, Stiehm ER. T-cell immunodeficiency disorders. In: Stites DP, Terr AI, Parslow TG, eds. Medical immunology, 9th edn. Stamford, USA: Appleton & Lange, 1997: 345–48.

2 Borzy MS, Ridgway D, Noya FJ, Shearer WT. Successful bone marrow transplantation with split lymphoid chimerism in DiGeorge syndrome. *J Clin Immunol* 1989; 9: 386–92.

3 Goldsobel AB, Haas A, Stiehm ER. Bone marrow transplantation in DiGeorge syndrome. *J Pediatr* 1987; 111: 40–41.

4 Maarkert ML, Hummell DS, Rosenblatt et al. Complete DiGeorge syndrome: persistence of profound immunodeficiency. *J Pediatr* 1998; 132: 15–21.

5 Bell EB, Sparshott SM, Drayson MT, Ford WL. The stable and permanent expansion of functional T cells in athymic nude rats after a single injection of mature T cells. *J Immunol* 1987; 139: 1379–84.

Division of Paediatric Oncology (D C Bowers; e-mail dcbowers@jhmi.edu); **Eudowood Division of Paediatric Immunology, Departments of Oncology and Paediatrics, Johns Hopkins University School of Medicine, Baltimore, MD 21207, USA**

Long-term outcome after thalamotomy for movement disorders in multiple sclerosis

Julie Hooper, Ian R Whittle

Sterotactic thalamotomy is an effective treatment for tremor in Parkinson's disease with long-term benefits.[1] After thalamotomy for tremor due to multiple sclerosis (MS), 90% of patients show immediate improvement, which remains in 70% of patients at 1 year, but longer-term outcome is not well known.[2] This issue is important since thalamic deep brain stimulation (DBS) is being investigated as an alternative treatment to thalamotomy for management of MS-related movement disorders.[3,4] Since the profile of patients with MS chosen for either thalamotomy or thalamic DBS is probably similar, and there are important clinical, management, and health economic implications to DBS,[3,4] we reassessed the clinical status and functional outcomes of ten patients with MS who underwent thalamotomy between December, 1989, and October, 1994. We aimed to find out outcomes after 1 year in movement disorders after thalamotomy and to ascertain the general clinical status of the patients.

All ten patients had a form of cerebellar tremor that w distinguished clinically into rubral tremor, characterised b severe postural tremor affecting the head, trunk, and upp limbs with a supradded action/intention component th was present during volitional limb movements, or a isolated action/intention tremor. All patients were severe disabled by the movement disorders and had no function use of their affected upper limb. After compute tomography-guided ventrolateral thalamotomy, brachi tremor was decreased in nine patients immediately after th operation.[5] In patients with severe rubral tremor, none ha complete abolition of their movement disorder, an although it decreased in most tremor remained disablin because of the unmasking or persistence of cerebella disease. At 1 year follow-up, only three patients, who ha the best preoperative Bartel scores, had improved functio (patients 4, 5, and 10). At final follow-up median 5 months after surgery) only six patients remained alive, an one (patient 10) still had improved function (table).

These findings strongly suggest that in many patient onset of severe movement disorders is followed by progressive functional decline, and even death, due to MS Also, although stereotactic surgery might be temporaril beneficial, a long-term impact is unlikely, mainly becaus of additional damage to the central nervous system Adequate assessment of thalamic DBS in patients wit MS-associated movement disorders will require long-ter follow up. Thalamic DBS, which is a more flexible an non-lesional therapy than thalamotomy, will, howeve have only temporary effects if systemic functional declin due to MS is as seen in our patients.

This work was funded by the Multiple Sclerosis Society of United Kingdom and Northern Ireland.

1 Kelly P, Gillingham FJ. The long-term results of stereotaxic surgery and L-dopa therapy in patients with Parkinson's disease. *J Neurosur* 1980; 53: 332–37.

2 Haddow LJ, Mumford C, Whittle IR. Sterotactic treatment of tremor due to multiple sclerosis. *Neurosurg Q* 1997; 7: 23–34.

3 Geny C, Nygen J-P, Pollin B, et al. Improvement of severe postural cerebellar tremor in multiple sclerosis by chronic thalamic stimulation. *Mov Disord* 1996; 11: 489–94.

4 Whittle IR, Hooper J, Pentland B. Thalamic deep brain stimulation for movement disorders due to multiple sclerosis. *Lancet* 1998; 351: 109–10.

5 Whittle IR, Haddow LJ. CT guided thalamotomy for movement disorders in multiple sclerosis: problems and paradoxes. *Acta Neurochir* 1995; 64 (suppl): 13–16.

Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, UK (I R Whittle)

Patient	Age (years)	MS subtype	Duration (years)	Characteristics of tremor					Pre-operative status by Bartel index (0–20)	Current status	
				Duration (months)	Severity	Type	Location	Initial result after surgery		Bartel index (0–20)	Follow-up (months after surgery)
1	43	Chronic progressive	7	12	Severe	Rubral	Head, trunk, upper limbs	Good	4	Dead	14
2	62	Chronic progressive	13	20	Severe	Action-intention	Left upper limb	Unchanged	8	3	73
3	38	Chronic progressive	6	6	Severe	Rubral	Head, trunk, upper limbs	Good	8	3	62
4	36	Chronic progressive	4	36	Severe	Rubral	Head, trunk, upper limbs	Good	8	Dead	9
5	32	Chronic progressive	2	20	Severe	Rubral	Head, trunk, upper limbs	Good	8	7	61
6	30	Chronic progressive	13	7	Severe	Rubral	Head, trunk, upper limbs	Good	8	3	56
7	35	Relapsing-remitting	17	20	Severe	Rubral	Head, trunk, upper limbs	Good	9	3	55
8	34	Chronic progressive	3	19	Severe	Rubral	Head, trunk, upper limbs	Good	8	Dead	16
9	32	Chronic progressive	3	15	Severe	Rubral	Head, trunk, upper limbs	Good	7	Dead	20
10	50	Relapsing-remitting	7	84	Severe	Action-intention	Right upper limb	Excellent	10	18	44

Table 1: **Characteristics of patients**

Sublingual oestrogen treatment of postnatal depression

Antti J Ahokas, Saija Turtiainen, Marjatta Aito

Postnatal depression has been estimated to affect over 10% of women with sequelae for the mother, marital relationship, and infant's psychological development.[1] Depression can be severe and resistant to psychotherapy and antidepressant drugs. Therefore, safe and rapidly effective therapies are needed,[2] with likely association to the cause of depression. Oestrogen has been shown to be effective in the treatment of postnatal depression.[3] We report two consecutive cases fulfilling the ICD-10 criteria of depression with postpartum onset admitted to the psychiatric duty outpatient unit who responded successfully to sublingual 17-β oestradiol monotherapy. We measured serum oestradiol by radioimmunoassay at baseline and weekly during follow-up. The treatment effect was evaluated by the 10-item Montgomery-Åsberg Depression Rating Scale (MADRS), scores 0–6.

A 30-year-old woman (case 1) had no personal or family history of mood disorders, and the relationship with her husband was stable. During the second week after delivery of her first baby she reported anxiety and sleep disturbances. Over the subsequent weeks she became more depressed, and reported inner tension, irritability, broken sleep, reduced appetite, and concern about her baby. Her family physician prescribed oxazepam 15–30 mg and counselling support was given with only temporary help. 2 months after delivery, the symptoms increased until she felt almost chaotic and came to the psychiatric duty outpatient unit, where severe postnatal depression was diagnosed (MADRS total score 43). Her serum concentration of oestradiol was 140 pmol/L, but other routine blood tests including thyroid function were within normal limits. With ethical committee approval and informed consent, she was given 17-β oestradiol (Estrofem, Novo Nordisk, Bagsvaerd, Denmark) 1 mg sublingually four times daily during the first week and 1 mg three times daily over the following week (table). After 1 week of treatment she was more optimistic and after 2 weeks reported being almost free of symptoms.

A 27-year-old teacher (case 2) had no history of psychiatric illness and a stable family situation. After her first delivery 3 years ago she felt tired but not depressed. 2 weeks after her second childbirth she began to feel depressed, anxious, and had broken sleep. Her symptoms progressed until 5 months after delivery when she felt unable to take care of the children and herself. Routine laboratory tests including thyroid function were within the normal range, apart from serum oestradiol which was 23 pmol/L. With informed consent, sublingual 17-β oestradiol was given 1 mg four times daily (table). After 2 weeks she was happy and reported to be without symptoms.

	Week			
	0	1	2	3
Case 1				
MADRS	43	19	2	0
Oestradiol	140	300	540	370
Case 2				
MADRS	39	17	1	0
Oestradiol	23	240	810	..

..=not measured.

MADRS total scores and oestradiol concentration (pmol/L) during treatment

Our method is based on measuring the serum concentration of oestradiol and replacing the deficiency with physiological oestradiol, while monitoring oestradiol to ensure adequate dosage. The sublingual route has several advantages: it avoids first-pass metabolism and the non-compliance[4] associated with transdermal oestrogen therapy. Furthermore, it offers rapid but short duration of action, thus mimicking the natural pulsatile ovarian function. These findings and the connection between oestrogen and serotonin[5] may have aetiological relevance to postnatal depression.

1 Cox JL, Murray D, Chapman G. A controlled study of the onset, duration and prevalence of postnatal depression. *Br J Psychiatry* 1993; **163:** 27–31.

2 Murray D. Oestrogen and postnatal depression. *Lancet* 1996; **347:** 918–19.

3 Gregoire AJP, Kumar R, Everitt B, et al. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996; **347:** 939–33.

4 Hall G, Spector T. The use of oestrogen replacement as an adjunct therapy in rheumatoid arthritis. In: Berg G, Hammar M, eds. Modern management of menopause. London: Parthenon Publishing Group, 1994: 369–75.

5 Fink G, Summer BEH. Oestrogen and mental state. *Nature* 1996; **383:** 306.

Department of Psychiatry, University of Helsinki, Fin-00260 Helsinki, Finland (A J Ahokas); **and Adnex Research Centre of Gynaecology, Helsinki**

Thalamic deep-brain stimulation for movement disorders due to multiple sclerosis

Ian R Whittle, Julie Hooper, Brian Pentland

Since 1980 when deep-brain stimulation (DBS) was first described for movement disorders,[1] there have been substantial technical advances in DBS hardware and brain imaging. Thalamic DBS is an established treatment for Parkinson's disease[2] but its value in movement disorders due to multiple sclerosis (MS) is uncertain, although one study suggested good results in 69% of patients.[3] We are prospectively evaluating thalamic DBS in MS patients and report our preliminary results.

17 MS patients with disabling upper-limb-movement disorders underwent extensive clinical, movement disorder (with videorecording), neuroradiological (magnetic resonance imaging [MRI]), and neuropsychological assessments. Patients were deemed not suitable for DBS implant because of predominant postural axial tremor (n=4), severe associated neurological dysfunction (4), or minimum associated disability (1). Eight patients underwent stereotactic exploration of the ventrolateral thalamus, with computed tomographic guidance and the Brown-Robert-Wells stereotactic system. Only five of these patients had a thalamic quadripolar DBS electrode (Medtronic, Minneapolis, MN, USA) and programmable pulse generator (Itrel-II, Medtronic) implanted since in the other patients no thalamic target point that produced suppression of the movement disorder could be identified, despite extensive intraoperative physiological

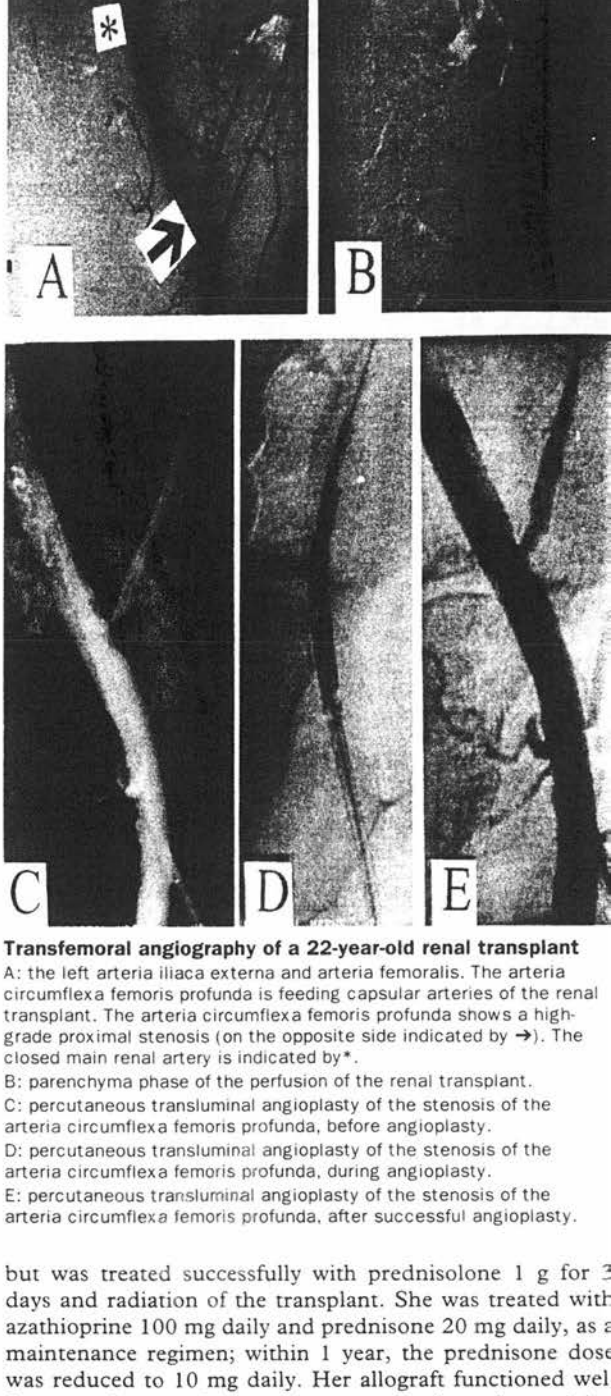
testing. One patient who showed no tremor suppression intraoperatively had a dramatic and sustained (6 months) improvement postoperatively, presumably because of a microthalatomoty effect. Our initial follow-up shows that the stimulus parameters for the DBS need regular adjustment to maintain optimum limb function.

These preliminary results have highlighted some difficulties. First, on clinical and neuroradiological grounds, it is impossible to predict which patients will benefit from this treatment. The movement disorders in all these patients were complex with ataxic, dysmetric, and tremorigenic components that affected the trunk and limbs. All the MRI scans showed diffuse hemispheric and brain-stem plaques with distortion of the thalami and widening of the third ventricle. Second, in five of these patients the neurophysiological responses usually elicited during stereotactic thalamocapsular stimulation were absent, despite preserved contralateral limb function. However, the responses to rostral midbrain stimulation (induced eye movement and pupillary changes) were preserved. Under these circumstances we have elected not to insert an electrode purely on anatomical localisation. Third, a comprehensive rehabilitation programme is required to support DBS insertion since the stimulators need programming adjustments and the patients need intensive physiotherapy and occupational therapy to relearn use of the limb. Fourth, mood disturbances occur after surgery either because it has failed or the result is not considered the expected panacea. This difficulty has occurred despite an extremely cautious approach to this therapy adopted by the research team. Further prospective evaluation of this treatment is essential to determine the long-term efficacy of thalamic DBS, its potential advantages compared with stereotactic thalamotomy,[4] and to avoid inappropriate application, unnecessary morbidity, and wastage of funds.

This study was supported by the Multiple Sclerosis Society of Great Britain and Northern Ireland.

1 Brice J, McLellan L. Suppression of intention tremor by contingent deep-brain stimulation. *Lancet* 1980; **315:** 1221–22.
2 Benabid AL, Pollack P, Gao D, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorder. *J Neurosurg* 1996; **84:** 203–14.
3 Geny C, Nguyen J-P, Pollin B, et al. Improvement of severe postural cerebellar tremor in multiple sclerosis by chronic thalamic stimulation. *Mov Disord* 1996; **11:** 489–94.
4 Haddow LJ, Mumford C, Whittle IR. Stereotactic treatment of tremor due to multiple sclerosis. *Neurosurg Quart* 1997; **7:** 23–34.

Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, UK (I R Whittle)



Transfemoral angiography of a 22-year-old renal transplant
A: the left arteria iliaca externa and arteria femoralis. The arteria circumflexa femoris profunda is feeding capsular arteries of the renal transplant. The arteria circumflexa femoris profunda shows a high-grade proximal stenosis (on the opposite side indicated by →). The closed main renal artery is indicated by*.
B: parenchyma phase of the perfusion of the renal transplant.
C: percutaneous transluminal angioplasty of the stenosis of the arteria circumflexa femoris profunda, before angioplasty.
D: percutaneous transluminal angioplasty of the stenosis of the arteria circumflexa femoris profunda, during angioplasty.
E: percutaneous transluminal angioplasty of the stenosis of the arteria circumflexa femoris profunda, after successful angioplasty.

Severe hypertension 22 years after renal transplantation

Martin Tepel, Ulf Laufer, Dieter Liermann, Walter Zidek

A 49-year-old woman was admitted to our department because of hypertensive urgency and increasing serum concentrations of creatinine. 22 years earlier she had received a cadaveric renal transplant for renal failure due to chronic pyelonephritis. She had been dialysed for 14 months, during which time she underwent bilateral nephrectomy; tissue from the latter procedure showed end-stage renal disease consistent with chronic pyelonephritis.

The cadaveric renal transplant had a cold ischaemic time of 17 h and showed a splicing of the renal artery into two small vessels. During the transplantation, a thrombosis of the main renal artery was observed and a second anastomosis of the renal artery had to be made. An acute rejection episode occurred 3 weeks after transplantation, but was treated successfully with prednisolone 1 g for 3 days and radiation of the transplant. She was treated with azathioprine 100 mg daily and prednisone 20 mg daily, as a maintenance regimen; within 1 year, the prednisone dose was reduced to 10 mg daily. Her allograft functioned well for several years; her serum concentration of creatinine ranged from 88 μmol/L to 106 μmol/L. 12 years later, her serum creatinine concentration rose to 159 μmol/L, and a renal-graft biopsy showed chronic tubulointerstitial rejection and focal scarring with changes indicative of chronic vascular rejection. Cyclosporin A was administered for 12 months but was discontinued because of side effects. Because she developed severe hypertension, the patient was treated with several antihypertensive drugs including furosemide, metoprolol, dihydralazin, and clonidine.

On physical examination, the patient was an alert cooperative woman; her systolic/diastolic blood pressure was 200/120 mm Hg, pulse 80 beats per min and regular and she was afebrile. Abdominal examination revealed a

Rater Reliability of Fahn's Tremor Rating Scale in Patients With Multiple Sclerosis

Julie Hooper, BSc, Robert Taylor, PhD, Brian Pentland, MD, Ian R. Whittle, MD

ABSTRACT. Hooper J, Taylor R, Pentland B, Whittle IR. Rater reliability of Fahn's Tremor Rating Scale in patients with multiple sclerosis. Arch Phys Med Rehabil 1998;79:1076-9.

Objective: Assessment of movement disorders in patients with multiple sclerosis (MS) is difficult because of the complex nature of the movement disorders. The aim of this study was to determine the reliability of Fahn's Tremor Rating Scale (FTRS) in assessing movement disorders in patients with MS.

Method: Videos were made of 10 patients with MS showing their rest, postural, action/intention, and goal-related movement disorders as well as their performance of spirometry, a volumetric task, and timed functional tasks. Ratings of tremor were carried out by one rater on two occasions 3 months apart and by 8 raters on one occasion using FTRS.

Results: Intrarater reliability was generally very good, with no significant "drift" in ratings over time. Interrater reliability was generally good, with some variation in interpretation of scoring criteria that may reflect raters' backgrounds.

Conclusion: The FTRS is a reliable and potentially useful tool with which to assess movement disorders in patients with MS.

TREMOR AND OTHER movement disorders are recognized features of multiple sclerosis (MS) and can be both distressing and disabling. In their series of 656 patients, Kraft and colleagues[1] reported tremor in 27%, in half of whom it was associated with difficulties in performing activities of daily living. Various treatments for tremor have been described, including oral medication, the use of weights applied to the wrists, and stereotactic surgery.[2,3] Descriptions of such therapies have used a range of ad hoc scales to measure tremor response, but at present no validated scale is available.[3] This partly is in contrast to experience with both essential and Parkinsonian tremor, for which standardized scales exist,[4-7] and reflects the complexity of the movement disorders associated with MS. As part of a prospective study of thalamic deep brain stimulation as a treatment for movement disorders in MS, we decided to use a modification of the Fahn Tremor Rating Scale (FTRS) as a measure of the tremor. To evaluate the applicability of the FTRS in this cohort, studies of both the intrarater an interrater reliability of the FTRS in patients with moveme disorders due to MS were undertaken.

PATIENTS AND METHODS

Patients. Ten patients who fulfilled the criteria for defini MS[8] participated in the study. The mean duration of disease w 11 years (range, 6 to 19 years). There were 3 men and 7 wome with a mean age of 40 years (range, 31 to 56). All we right-handed. Seven were wheelchair-bound and the remainir three could walk short distances but had significantly impaire mobility. All 10 patients underwent a full neurologic examin tion from which the expanded disability status scale scor (EDSS) was obtained. The mean EDSS was 6.5 (range, 4.5 8.5). All patients had severe postural and intentional tremors.

Videorecording. Videorecordings of the patients being a sessed were made according to a standardized protocol. Th videorecording included the following components: (1) " rest" in supported sitting and/or supine lying; (2) performir specific purposeful movements such as voluntary movemen of the head, drinking from a cup (held by both the examin and, when possible, the patient), maintaining the upper limbs certain positions and performing intentional movements and th finger/nose test; (3) attempting to sit unsupported for 6 seconds, standing unsupported for 10 seconds, and walking meters; (4) performing spirometry; (5) performing a volumetr test; (6) performing hand writing and card turning from th Jebsen Test of Hand Function.[10] A composite and edited vide of the patients performing these tasks was compiled an distributed to each rater who used the following scales.

The FTRS. The FTRS comprises three parts—A, B and Part C assesses functional disability as scored by the patient an consequently was not included in this reliability study. Min modifications were made to the FTRS from its original descri tion in 1988. Goal-related tremor was assessed separately rath than being grouped with action/intention tremor, and the lir drawing tests were omitted because of the severity of disabili in the patient group.

Part A of the FTRS included subjective rating of the severi of tremor for the head, trunk, right upper extremity, and le upper extremity for rest tremor, postural tremor elicited with t arms maintained in an extended position and a flexed positio action/intention tremor, and goal-related tremor. In total, th part of the assessment required 18 separate scores (table 1). F each of these subtests or observations the tremor was defin as: 0 = none; 1 = slight, may be intermittent; 2 = modera amplitude, may be intermittent; 3 = marked amplitude; and 4 severe amplitude.

Part B of the FTRS included subjective rating of tas performed with each hand. These included drawing of Arc med es' spirals (spirometry) and pouring water from one cup another (volumetric test). The quantification of spirometry w based on the crossing of the lines in the figure: 0 = normal; 1 slightly tremulous; 2 = moderately tremulous or crosses lir frequently; 3 = accomplishes task with great difficulty, ma errors; and 4 = unable to complete drawing. There was le space between the lines in the smaller of the two spirals, maki

From the Department of Clinical Neurosciences, Western General Hospital, Edinburgh, United Kingdom.

Submitted for publication December 18, 1997. Accepted in revised form March 12, 1998.

Supported by the MS Society of Great Britain and Northern Ireland.

Presented in part at 13th Congress of European Society of Stereotactic Functional Neurosurgery, 1996, Milan, and at 4th Annual Meeting of British Neurosurgical Research Group, April 1997, Newcastle.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors or upon any organization with which the authors are associated.

Reprint requests to Julie Hooper, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU United Kingdom.

0003-9993/98/7909-4769$3.00/0

Table 1: Statistical Values for Intrarater and Interrater Reliability Using FTRS to Assess Aspects of Movement Disorders in Patients With MS

Rating of Tremor	Intrarater Reliability: Spearman Correlation Coefficient	Intrarater Reliability: Wilcoxon Matched Pairs Signed Ranks Test (p Value)	Interrater Reliability: Average Spearman* Correlation Coefficient	Interrater Reliability: Friedman ANOVA (p Value)
Head tremor				
1. Rest	Not computed	1	.28	.002
2. Postural	.92	.56	.87	.004
3. Action/ intention	.97	.32	.82	.001
4. Goal	.85	.41	.77	.002
Trunk tremor				
5. Rest	Not computed	1	.01	.02
6. Postural	.64	1	.84	.166
7. Action/ intention	.93	.16	.76	.001
8. Goal	.72	.68	.72	.008
Right upper limb				
9. Rest	Not computed	1	.22	.001
10. Postural a	.99	.16	.87	.009
11. Postural b	.99	.32	.86	.489
12. Action/ intention	.92	1	.87	.001
13. Goal	.94	.16	.84	.009
Left upper limb				
14. Rest	Not computed	1	.19	.001
15. Postural a	.94	1	.86	.001
16. Postural b	.99	.32	.9	.005
17. Action/ intention	.93	1	.73	.001
18. Goal	.81	.66	.69	.003
Upper limb tasks				
19. Large spiral—right	1	1	.93	.005
20. Large spiral—left	.99	.32	.81	.232
21. Small spiral—right	1	1	.93	.292
22. Small spiral—left	.87	.16	.92	.912
23. Pouring—right	1	1	.97	.195
24. Pouring—left	.99	1	.99	.333

Correlations above 0.7 are considered high and above 0.9 are considered very high.
*Derived from Kendall's coefficient of concordance.

the task more difficult. Pouring water from one cup to another was also quantified. Cup size and amount of water used in the test were specified to ensure consistency between assessments. The amount of water spilled is the basis for the severity grading: 0 = normal function; 1 = more careful than a person without tremor, but no water is spilled; 2 = spills a small amount of water (up to 10% of total amount); 3 = spills a considerable amount of water (>10% to 50%); 4 = unable to pour water without spilling most of the water. This part of the FTRS involved assessment of 6 separate tasks (table 1). In total, 24 separate scores were obtained for each patient.

Assessment of the patients. For the intrarater assessmen one rater (JH) rated the 10 patients on each of the 24 tests o two separate occasions 3 months apart. For the interrate assessment 8 raters (3 medical practitioners and 5 physiothera pists) were asked to study the scoring guidelines and instruc tions for using the FTRS scale. They then watched th videotape of the 10 patients and rated each patient's tremor o each of the 24 tests. Six raters worked in the clinical neurosci ences in different units within Edinburgh and two of the rater were physiotherapy lecturers involved in teaching neurology a undergraduate and postgraduate levels. None of the raters ha any experience using the FTRS before the study. All rating were performed independently.

Statistical analysis. Nonparametric statistics were use throughout. Intrarater or test-retest reliability data were ana lysed using Spearman correlations and Wilcoxon matched-pair signed ranks tests. Interrater reliability data were analyse using Kendall's coefficient of concordance (from which aver age interrater Spearman correlations can be derived) an Friedman analysis of variance (ANOVA). The data wer analyzed using SPSS for Windows.[a]

RESULTS

All raters completed the requisite assessments and did no comment upon any particular difficulties. Once raters familiar ized themselves with the scale, it was easy to use and tremo was rapidly assessable.

Intrarater Reliability

The intrarater reliability coefficients (Spearman correlatio coefficient [r]) are shown in table 1; and range from .85 to .9 for the different categories of head tremor, .64 to .93 for trun tremor, .92 to .99 for the right upper limb tremor, .81 to .99 fo the left upper limb tremor, and .87 to 1 for the tremor evider when performing upper limb tasks (spirometry and volumetri test). Levels of reliability are high except when certain catego ries of tremor in the trunk are being assessed (postural tremo $r = .64$ and goal related $r = .72$).

Correlations could not be computed for rest tremor of any o the four body parts because nearly all patients received identica ratings of 0, indicating no rest tremor in these MS patients.

The Wilcoxon matched pairs signed ranks tests showed n significant differences (all p values >.05) between the level o ratings of tremor on any of the 24 measures when rated by th same rater on two different occasions 3 months apart, indicatin that there was no "drift" to more stringent or more lenie rating (table 1).

Interrater Reliability

The average value of the Spearman correlations between a possible pairs of raters was calculated via Kendall's coefficie of concordance to determine the overall agreement for eac measure among the eight raters' sets of scores. The interrat reliability coefficients range from .69 to .99. The scores for re tremor, where nearly all ratings on these measures were ze ranged from .01 to .28, confirming the absence of rest tremor this patient sample.

Friedman ANOVA was used to establish whether some rate scored patients more strictly or more leniently than other rate Results (table 1) showed several significant differences in t rating levels (those with p values <.05) indicating that althou there was good agreement among raters on ranking of trem severity in different patients, raters varied in their interpretati of the severity of tremor required for allocation to given poin on the 0-to-4 scale. Subsequent analysis showed that the tw

non–medically qualified academic raters, who are not in regular clinical practice, tended to rate tremor as more severe than did the medical staff and the physiotherapists, who tended to differ little among themselves.

DISCUSSION

The aim of this study was to determine the reliability of a slightly modified FTRS when rating the severity of tremor in various parts of the body in patients with movement disorders due to MS. Raters found the FTRS simple to use when evaluating an edited video of the patients performing ad hoc tasks. In general, the results demonstrate very good intrarater and good interrater reliability, although there were variations in rater scores of tremor in different body regions. Assessment of tremor in the trunk showed a lower intrarater and interrater reliability, although it still showed a satisfactory level of agreement. This difficulty in scoring truncal tremor may be because there is less emphasis in the guidelines on how to assess tremor in the trunk. In contrast, scores for tremor on the upper limb tasks showed good reliability (correlation coefficients were all >0.8). In particular, spirometry provides a convenient measure of the disability caused by a movement disorder that is also consistently graded. Furthermore, spirometry is a quick and practical way of assessing and reassessing patients in the clinic or by postal survey, especially as the spiral drawings in FTRS have been standardized.

The extent of rater agreement in this study is a result not only of the inherent qualities of the assessment scale but also of features of the setting and characteristics of the individual raters. Standardized testing is essential to permit comparison between measurements. In this study the patients were assessed using a standardized assessment protocol, a specified scoring procedure, under the same environmental conditions, with consistent directions. The video tape could be rerun as necessary to help assessment and assist the raters to reach a judgement on the severity of a patient's tremor. When making this judgement, raters are influenced by their own experiences, expertise, knowledge, and personal bias. This contributes to the differences in rating levels found among raters and suggests that in clinical studies it is advisable for either the same person or members of the same occupational group to perform the ratings of tremor. Because of the diffuse nature of the disease, MS patients will often have other associated neurologic symptoms that may influence the assessment. For example, it is difficult to assess postural tremor of the trunk if the patient is unable to sit unsupported because of truncal weakness. It is also difficult to assess action/intention and goal-related tremor in the trunk if there is no active, intentional movement. The cohort of patients in this study was determined by the severity of their movement disorders, as only patients with moderate to severe movement disorders caused by MS were referred for thalamic deep brain stimulation.

The variability in results reflects some of the practical difficulties of assessing movement disorders in MS where movement disorders are complex manifestations of cerebellar, brain stem, diencephalic, and subcortical white matter disease. Classification of tremor in MS is not straightforward for clinicians.[11] Currently, clinicians favor the classification of tremor into rest and action categories, the latter being subdivided into postural, action, intention, and goal-related types, or according to the etiology of the underlying diseases with which a particular tremor is associated. Although these approaches have been widely adopted, in practice clinicians experience difficulties in distinguishing the intention and action components of tremor, particularly if a postural component is also present. This is complicated further in patients with MS who may also have an associated cerebellar syndrome.

It is difficult clinically to define the boundaries of action, intention, and goal-related tremor and to differentiate between these types of tremor and dysmetria. What different clinicians mean by intention tremor is also questionable; recently, four neurologists with a special interest in movement disorders were asked to classify the upper limb tremors of 20 videotaped patients. Before the assessments, the four agreed on the definitions of action and intention tremors. The results for interrater reliability showed that there was very poor agreement among the assessors concerning which of the patients had action or intention tremor and even less agreement on the severity of these two components of tremor.[12] In clinical practice it may be better not to attempt to distinguish between action and intention tremor. Intention tremor, also known as terminal tremor, is the pronounced exacerbation of action tremor (tremor evident during movement) towards the end of a goal-directed movement. For this study we found it was easier to assess action tremor along with intention tremor by asking the patient to perform the widely used finger/nose test. Goal-related tremor occurs to any significant extent during the performance of a functional task. We assessed goal-related tremor by observing the patient performing spirometry, pouring, and the subtests of the Jebsen Test of Hand Function.

There are guidelines for using the FTRS scale but the emphasis is on assessing tremor in the upper limbs. Patients with MS frequently present with a cerebellar syndrome that usually affects the proximal more than distal muscles and the head and trunk may also be involved. In the past this type of tremor was frequently termed "rubral tremor" and characteristically results in movements being wild and flailing. Hallet[13] recommends abandoning the term because of the inaccurate pathophysiology that it implies and refers to this type of tremor as severe postural cerebellar tremor. Many MS patients have severe postural cerebellar tremor and Hallet has observed that this type of tremor "persists or worsens with goal directed movement and it is associated with dysmetria." For this reason in this study we scored goal-related tremor separately from action/intention tremor. Expansion of the guidelines and clarification of assessment instructions, particularly as regards the head and trunk, may improve ease of use and reliability. Assessments of rest tremor in different areas of the body are not appropriate tests for this group of patients since it is rare in patients with MS and therefore could be omitted from the scale. It might, however, be useful to keep this test in the assessment if the scale is to be used with other patient samples.

Standardized assessment is essential to permit comparison between raters and between studies. A training video showing patients with varying severity of tremor being assessed using FTRS would help to calibrate the judgement of raters and provide appropriate training. Adequate reliability is a prerequisite but obviously not a guarantee of adequate validity. The FTRS evidently has high reliability but further work should elaborate upon the other aspects of validity.

CONCLUSIONS

A composite of the FTRS provides a simple, concise 24-item scale for evaluating movement disorders in MS. Interrater and intrarater reliability scores obtained in this study show that it can be used with confidence in a clinical setting and that it may have important clinical utility. Raters, however, should be familiar with the guidelines for using the scale and preferably should have experience in the field of clinical neurology. It is preferable for research purposes that one rater performs the

assessments, because intrarater reliability was higher than interrater reliability.

The potential utility and reliability of the scale is evidently high, but more work is needed to establish its validity further and to expand the definitions and guidelines so that it relates specifically to evaluating the complex movement disorders seen in patients with MS. Treatment for disabling tremor in MS patients cannot be properly evaluated without reliable and valid measures of tremor.

Acknowledgments: We are grateful to our colleagues who rated the videos of the patients.

References

1. Kraft GH, Freal JE, Coryll JK. Disability, disease duration and rehabilitation service needs in multiple sclerosis: patient perspectives. Arch Phys Med Rehabil 1986;67:164-8.
2. Matthews WB. Treatment. In: Matthews WB, Compston A, Allen IV, Martyn CN, editors. McAlpine's multiple sclerosis. 2nd ed. Edinburgh: Churchill Livingstone; 1991. p. 251-98.
3. Haddow L, Mumford C, Whittle IR. Stereotactic treatment of tremor due to multiple sclerosis. Neurosurg Q 1997;7:23-34.
4. Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic A, Tolosa E. Parkinson's disease and movement disorders. Munich: Urban and Schwarzenberg; 1988. p. 225-34.
5. Benabid A, Pollak P, Gervason C, Hoffman D, Gao D, Hommel M. Long term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991;337:403-6.
6. Blond S, Caparros-Lefebvre D, Parker F, Assaker R, Petit H, C J-D, et al. Control of tremor and involuntary movement disc by chronic stereotactic stimulation of the ventral interme thalamic nucleus. J Neurosurg 1992;77:62-8.
7. Bain PG, Findley LJ, Atchison P, Behari M, Vidailhet M, G M, et al. Assessing tremor severity. J Neurol Neurosurg Psych 1993;56:868-73.
8. Poser CM, Paty DW, Scheinberg L, McDonald I, Davis F, Ebe et al. New diagnostic criteria for multiple sclerosis: guidelin research protocols. Ann Neurol 1993;13:227-31.
9. Kurtzke J. Rating neurological impairement in multiple scle an expanded disability status scale (EDSS). Neurology 198 1444-52.
10. Jebsen R, Taylor N, Trieschmann R, Trotter M, Howard L objective and standardized test of hand function. Arch Phys Rehabil 1969;50:311-9.
11. Elbe RJ, Koller WC Tremor. Baltimore: The John Ho University Press; 1990.
12. Francis D, Bain P, Swan A, Hughes R. An assessment of disa rating scales used in multiple sclerosis. Arch Neurol 1991;48 301.
13. Hallet M. Differential diagnosis of tremor. In: Vinken PJ, Br GW, Klaeans HL, editors. Handbook of clinical neurology Vol 49. Amsterdam: Elsevier; 1986. p. 583-95.

Supplier

a. SPSS 6.1 for Windows; SPSS, Inc., 444 North Michigan Av Chicago, IL 60611.